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NOTE ON PLACENTATION IN QUADRUPLET AND TRIPLET PREGNANCY[1]

J. WHITRIDGE WILLIAMS

From the Obstetrical Department of the Johns Hopkins Hospital and University

While twins have been born once to every 91 patients admitted to our service, triplets occur but rarely, and as yet no quadruplet birth has been observed. Hellin promulgated an inaccurate, but easily remembered, formula for approximating the incidence of the several types of multiple pregnancy, and, assuming that twins occur once in every 80 conceptions, he estimates that the probable frequency of triplets and quadruplets can be obtained by squaring that number, or by raising it to the third power, respectively.

Thus, twins, 1 to 80

triplets, 1 to $80 \times 80 = 1$ to 6,400

quadruplets, 1 to $80 \times 80 \times 80 = 1$ to 512,000

In other words, quadruplets are born approximately once in a half million labors, and any occurrence which is so infrequent deserves comment. In this communication I shall describe the placental relations in such a case, as well as in six cases of triplet pregnancy.

The authors of the sixteenth and seventeenth centuries had noticed in twin pregnancies that one might have to deal either with two separate placentae or with a single organ, and in the latter event that definite anatomical differences could sometimes be detected according to the sex of the children. When of opposite sex, the children were always separated by a partition wall, whereas when of the same sex, this was sometimes lacking. Viardel naïvely regarded the difference as an indication of a divine interest in safeguarding the morals of twins *in utero*, but it was not until after the discovery of the ovum by von Baer, as well as the relationship which it bears to the formation of the chorion and amnion, that the arrangement of those membranes was utilized to determine whether twins attached to a single placenta had been derived from two separate ova or from a single

[1] Received for publication August 9, 1926.

ovum. It is now universally admitted that single ovum, or identical, twins are always enclosed within a single chorion, but that an individual amnion surrounds each twin. In other words, the partition wall separating them consists of two layers of amnion, and in the rare instances in which it is lacking, it is assumed that it had originally existed and had later become destroyed.

At present in all well regulated obstetrical services, whenever one has to deal with twins of the same sex attached to a single placenta, the attempt is made to determine whether they are of the single or double ovum variety, by ascertaining whether the partition wall consists of two or of four membranes. If the former, both membranes are amnion, whereas in the latter event we have to deal with two amnions and two chorions. As the membranes are usually easily separable, such a determination can ordinarily be readily made, but if any uncertainty arises, microscopic examination will remove all doubt. Studied in this way, we have found that we had had to deal with single ovum or identical twins in 24 per cent of 280 cases of twin pregnancy.

While it is probable that a septuplet birth occurred in the year 1600 in Hameln an der Weser, where a mural tablet commemorates the event, nothing is known concerning its placental relations. The same applies to the rare cases of sextuplet pregnancy. More is known concerning quintuplet pregnancy, and de Blécourt and Nijhoff, in a monographic study, state that in their case three ova were concerned, as was evidenced by the presence of three placentae—two separate single ones and a single ovum triplet placenta. There is likewise scant information concerning the relations in quadruplet pregnancy, but Saniter, Sunde and others have carefully studied the conditions obtaining in triplets.

This being the case, I thought that it might be interesting to report the conditions observed in our cases, a brief description of which follows.

I. FOUR EGG QUADRUPLET PREGNANCY WITH TWO PLACENTAE

We are indebted to Dr. Meyer Ephraim of Baltimore for the placentae from this case, as well as for the information concerning the

clinical course of the labor. The 38-year old patient, (C. W., 1839), fell into her ninth labor on November 7, 1923, several weeks before the calculated date. No history of previous multiple pregnancies was obtainable. After an easy labor the first two children—a girl and boy—were expelled spontaneously. As the uterus appeared exhausted after that effort, pituitrin was administered, which promptly resulted in the birth of a second girl, which was soon followed by the expulsion of a third girl. The latter was extruded along with its placenta and was enclosed within the intact membranes which were ruptured artificially in order to free it. Following this, the large

FIG. 1. FUSED THREE EGG PLACENTAE FROM A QUADRUPLET PREGNANCY × ½

fused placenta was expressed without difficulty. The children were alive and varied between 4½ and 5 pounds in weight. All of them lived beyond the puerperium but eventually died, the last one succumbing at the age of 8 months.

Dr. Ephraim sent the afterbirth to the Clinic, when it was found to consist of two parts—a single placenta belonging to the girl born with a "caul" and a large triple one—the two together weighing 1190 grams. The single placenta was approximately round, measured

17 × 16 × 1.5 cm. in its various diameters, with the cord inserted eccentrically, and presented no abnormalities upon either its foetal or maternal surfaces. Subsequent microscopic examination revealed normal conditions.

As two girls and a boy had been attached to the larger placenta, it was apparent that more than one egg had been concerned in their production, and closer examination confirmed that conclusion. The fused placenta was quadrilateral in outline and measured 41 × 18 × 2 cm. in its several diameters (Fig. 1). The maternal surface was smooth and showed no evidence of fusion or of subdivision. On the foetal surface, however, three placental areas are noted. That to the left is kite-shaped, and 24 × 15 cm. in size. The cord is inserted at its outer margin, and one of its large vessels courses freely through the membranes to return to the foetal surface of the placenta at its smaller pole. The central area is roughly quadrilateral in shape, measures 19 × 13 cm., and presents no apparent abnormality; while the cord is inserted velamentously at its lower right hand corner. The third, or right hand area, is oval in shape, measures 18 × 12 cm. and has its cord inserted eccentrically. The membranes separating the three areas are thick, and there is no anastomosis between the vessels of the several areas.

Upon dissecting the membranes, as well as from their microscopic study, it is found that each partition wall consists of four layers—two amnions and two chorions. Consequently the evidence is conclusive that we have to deal with a placenta resulting from the early fusion of three single ones, and that the quadruplets had originated from four separate ova and really represented a litter. Unfortunately, no data are available to indicate to which of the three areas of the fused placenta the male foetus had been attached.

Passing to the consideration of the conditions obtaining in triplet pregnancy, it is apparent that it may arise from the fertilization of three, two ova or one ovum, respectively, and that in all but the last event the placental relations may present several variations.

For example, in the three egg variety three eventualities are possible, so that one may have (a) three separate placentae, each with its own chorion and amnion; (b) two separate placentae, one single and the other fused, and representing a double ovum twin placenta; and

(c) a single placenta. In the third event three originally separate placenta have become fused, so that a single organ results with three foetal areas, each with their two layers of membranes. In two egg triplets, two eventualities are possible: (d) two separate placentae—one a single organ with its own chorion and amnion; and the other a single ovum twin placenta with one chorion and two amnions. In the second eventuality, (e) we have to deal with an early fusion of the two placentae mentioned under (d), so that a single organ results, with two chorions and three amnions. Finally, in one egg triplet pregnancy only one eventuality is possible, and that is (f) a single placenta, with a single chorion and three amnions.

In our material we have observed examples of four of the six possibilities, but we have not yet encountered specimens illustrating eventualities (a) and (f). The former undoubtedly occurs; and, after Saniter had described an example of the latter, Sunde, in 1925, was able to collect from the literature the description of 34 such placentae. Moreover, Weinstein by statistical methods has calculated that they should constitute 28 per cent of all triplet placentae.

I shall now pass on to a brief description of our own specimens.

II. THREE EGG TRIPLET PREGNANCY WITH TWO PLACENTAE

Figure 2 reproduces the conditions observed in a specimen, which I owe to the courtesy of my associate John G. Murray, Jr., as well as those obtaining in one of our own cases (Barker, O.O.S. 6897). In Murray's case (C.W., 1919) we had to deal with the live birth of a girl and two boys, varying in weight from 2250 to 2730 grams. The afterbirth consists of two placentae, one single and small, belonging to the girl, and the other large and fused. The former measures 14 × 16 × 2 cm., with the cord inserted somewhat eccentrically, and presents normal foetal and maternal surfaces. The fused placenta is somewhat egg-shaped, measures 16 × 22.5 × 2 cm., and its foetal surface is divided into two portions by a sickle-shaped membranous partition extending parallel to and 9 cm. above its larger pole. The attachment of the cords are clearly shown in the illustration. The maternal surface is smooth and shows no sign of fusion.

Dissection of the partition wall, as well as the microscopic examina-

tion of sections through it, shows that it is made up of two chorions and two amnions—in other words, that we have to deal with the fused placenta of double ovum twins, so that when we take into consideration the existence of the single placenta belonging to the girl, it is apparent that the triplets in this instance were derived from the fertilization of three separate ova. In our own case (Barker, O.O.S. 6897) the conditions were identical, except that we had to deal with the spontaneous birth of three male foetuses, all presenting by the breech and weighing 5775 grams in the aggregate. The placentae weighed 1050 grams.

FIG. 2. THREE EGG TRIPLET PREGNANCY WITH TWO PLACENTAE × ⅓

III. THREE EGG TRIPLET PREGNANCY WITH A SINGLE PLACENTA

Strictly speaking, we have not observed this eventuality, but as it obtained in the fused placenta in our quadruplet specimen, a glance at figure 1 will serve to elucidate the condition.

IV. TWO EGG TRIPLET PREGNANCY WITH TWO PLACENTAE

Figure 3 exemplifies this condition, and the specimen was obtained from an 18-year old colored primipara, who without apparent cause

aborted spontaneously May 28, 1924 (Connor, H. (13549)). The first foetus was born spontaneously and upon attempting to express the placenta, the second ovum surrounded by its placenta and membranes was expelled intact. This was immediately followed by the birth of a foetus compressus, and the process was concluded by the expulsion of the double placenta. All of the embryos were female, the two, whose hearts beat for a few minutes, each measured 25 cm. in length and weighed 385 grams, while the macerated one was 17 cm. long and weighed only 100 grams.

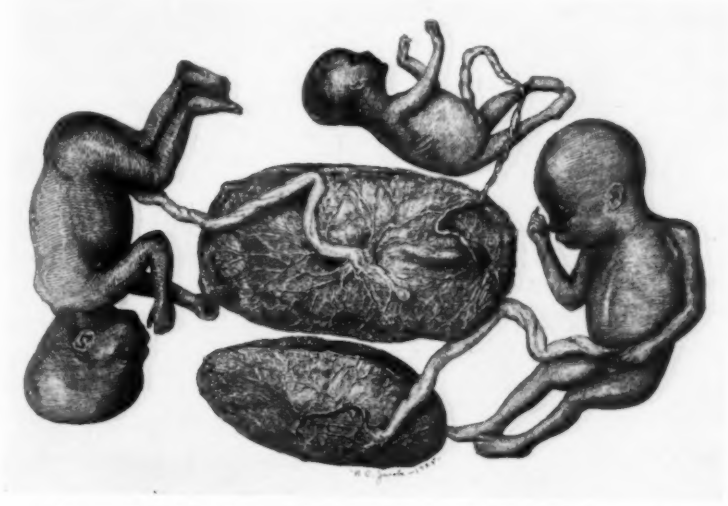

FIG. 3. TWO EGG TRIPLET PREGNANCY WITH TWO PLACENTAE $\times \frac{1}{4}$

Examination of the drawing shows that the embryos are still attached to their respective placentae. The single one belonging to the foetus at the right of the figure is pyriform in outline, measures $7 \times 14 \times 1.5$ cm., and weighs 135 grams. It has its own chorion and amnion and is normal both macro- and microscopically. The larger placenta to which the foetus compressus is attached measures $8 \times 18 \times 1.5$ cm., and weighs 195 grams. The portion of the foetal surface belonging to the healthy foetus is normal in appearance, while that corresponding to the foetus compressus is bloodless and

yellowish in color. One chorion and two amnions can be demonstrated. Definite anastomoses between the two circulations are present, and the figure gives a good idea of the degree of torsion to which the cord of the dead child had been subjected. Microscopic examination of the double placenta shows that the portion belonging to the living child is normal; while in the part belonging to the dead one varying degrees of infarct formation are present. Inflammatory changes in the chorionic membrane were also present. In this case it is apparent that we have to deal with a typical single pregnancy, in addition to single ovum twins, one of which had succumbed some time prior to the occurrence of the abortion.

Similar placental conditions were observed in a case of triplets delivered July 13, 1926 (Banoni, H. 16666)), except that the pregnancy had advanced to term, and that the foetus belonging to the single placenta was female, while the single ovum twins were male. In this case, also, the single ovum origin of the twin placenta was evidenced not only by the arrangement of the membranes, but also by the occurrence of anastomoses between the vessels of the two cords. It might be noted that the smaller placenta weighed 390 and the larger one 790 grams, and that the mother and her three children were discharged in good condition. Furthermore, it is interesting to note that a clinical diagnosis of twins had been made during the last weeks of pregnancy, but that an x-ray examination had failed to reveal the presence of the third child.

V. TWO EGG TRIPLET PREGNANCY WITH A SINGLE PLACENTA

Figure 4 depicts the conditions in this case (Phillips, H., 13,187), in which girl triplets were born to a 30-year old white III para. In this instance, antepartum examination showed the presence of twins and hydramnios, while the X-ray gave no indication of the existence of the third child. The first and third child were born spontaneously, while the second was delivered by version and extraction. The children varied from 2115 to 2715 grams in weight, aggregating 6150 grams, and were discharged in good condition.

The placenta was unusually large and heavy, measuring 29 $\times$ 23 $\times$ 4 cm. and weighing 1920 grams. Figure 4 shows that its foetal surface is divided into two parts of unequal area by a partition wall

made up of two chorions and two amnions. The smaller area is auricular in shape, with its cord attached near the partition. The larger area is roughly circular in outline with one cord attached near the partition and the other near the free border. Moreover, numerous anastomoses between the two sets of vessels are clearly visible. The conditions indicate beyond peradventure that we have to deal with the fusion of two placentae, one a typical single one and the other characteristic of single ovum twins. It should, however, be

FIG. 4. TWO EGG TRIPLET PREGNANCY WITH A SINGLE PLACENTA × ½

noted that the maternal surface was quite smooth, showed no trace of a furrow, which indicates that the fusion must have occurred early in pregnancy.

VI. TRIPLET PREGNANCY WITH SINGLE PLACENTA, BUT WITHOUT DATA AS TO ITS MODE OF ORIGIN

In this case, which occurred in 1903 (Scott, O.O.S. 1924), premature girl triplets—1700 to 1812 grams in weight—were born spontaneously

to a 28 year old colored III para and were all discharged in fair condition.

No careful study of the placental relations were made, the only note being that it was a single structure measuring 21 × 19 × 4 cm., and weighing 1125 grams. For this reason it is impossible to state whether it was derived from three or two ova, or from a single ovum.

OBSERVATIONS ON THE MENOPAUSE

I. The Basal Metabolism after the Artificial Menopause

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With the Technical Assistance of Ellen Patterson

From the Medical Clinic, School of Medicine, the Johns Hopkins University

In considering the nature of the symptoms of the menopause, natural or artificial, one is confronted by the fact that we lack a satisfactory objective criterion by which the general aspects of the menopause may be judged. Various ovarian preparations are administered empirically to women suffering from symptoms of the menopause, yet such therapy must necessarily be based upon a very uncertain footing so long as we have only the patients' stories as proof or disproof of the results.

The physiological action of various ovarian preparations has been studied carefully by a number of observers: the production of artificial oestrus cycles in ovariectomized animals by the administration of ovarian preparations has been of great aid in demonstrating the effect of such preparations upon the female genitalia.[1] It has been shown[2] that extracts of corpus luteum of a lipoid nature suppress ovulation, while ovarian and follicular fluids and ovarian residue extracts cause oestrus changes in the uterus and vagina. Allen and Doisy[3] have proved beyond doubt the efficacy of follicular extract of the ovary, given subcutaneously, in producing artificial oestrus cycles. It is of interest that the follicular fluid used by Allen and Doisy was obtained from hogs and cattle and produced results in the mouse and rat.

[1] Stockard, C. R., and Papanicolaou, G. N.: The Existence of a Typical Oestrus Cycle in the Guinea-Pig, with a Study of its Histological and Physiological Changes. *Am. J. Anat.*, 1917, xxii, 225.

[2] Papanicolaou, G. N.: The Production of Certain Distinct Types of Reactions by the Use of Ovarian Extracts. *Proc. Soc. Exper. Biol. and Med.* (N. Y.), 1924, xxii, 106.

[3] Allen, E., and Doisy, E. A.: An Ovarian Hormone. Preliminary Report. *Jour. Am. Med. Assn.*, 1923, 81, 819.

Such work is of great interest and value in estimating the potency of ovarian preparations upon the sexual apparatus: furthermore, preparations that have been proved active by such methods may be found to have a replacement value in the relief of symptoms of the menopause. It must be remembered, however, that the ovary is a very complex, as well as a cyclic structure, and it is extremely risky to attempt to translate such experimental data into the field of therapeutics of human beings.

Recently I have studied the basal metabolism of a number of women following the normal and artificial menopause. This was done with the hope that the many and contradictory data upon this subject might be explained, and that some light might be thrown upon the nature of the menopause and its associated symptoms.

A mass of work bearing upon this subject is found in the literature. In a recent review, DuBois[4] says: "We can agree . . . . that a total absence or diminished function of the sex glands only exceptionally causes a diminution in the oxidative processes." The literature upon which our present knowledge of the basal metabolism after castration is based is, however, so contradictory that Aub[5] concluded, as well as Bailey,[6] that the evidence in the literature favors the conclusion that a fall of metabolism does follow gonadectomy.

The work of Loewy and Richter[7] has received considerable attention in reviews of the subject. They quote Aristotle and Pliny upon castration of female animals, and also Galen, who said: "Female hogs after castration become swollen and fat." A female dog castrated by Loewy and Richter showed a drop in oxygen consumption per kilo of weight, per minute, of 18 per cent, in a period of two to six months. In the same time the weight had increased almost exactly 10 per cent. When "oöphorin" was given by mouth, the unit metabolism rose to a level higher than that before operation,

[4] DuBois, E. F.: Basal Metabolism in Health and Disease, Lea and Febiger, Phila. and N. Y., 1924.

[5] Aub, J. C.: The Relation of the Internal Secretions to Metabolism. *Jour. Am. Med. Assn.*, 1922, **79**, 95.

[6] Bailey, H.: Experimental Studies Following Oöphorectomy. *Am. Jour. of Obst. and Gyn.*, 1921, ii, 77.

[7] Loewy, A., and Richter, P. F.: Sexual Function und Stoffwechsel. *Arch. f. Physiol.*, Supplement Bd., 1889, 174.

falling again when it was discontinued. A few comments on this work should be made: first, the period of low metabolism occurred comparatively soon after operation: second, the rise of metabolism, associated with the eating of "oöphorin" may have been spontaneous. This assumption is even probable in view of the careful work of Durrant,[8] who fed daily a glycerine extract of whole sow's ovary for three weeks to eight doubly ovariectomized rats. Such feeding caused no increase in the voluntary activity of these rats, which is markedly reduced by ovariectomy.[9]

Luethje[10] castrated a female dog and compared its various metabolic processes with those of a normal control. In five months' time he found no significant difference between the CO_2 output of the two dogs.

A report which seems to support the view that a fall in metabolic rate follows castration is that of Murlin and Bailey.[11] Their results uphold the work of Loewy and Richter as to a reduction of the basal metabolism after castration. Removal of the ovaries in two bitches was followed by an increase in weight in both, and the lowering of metabolism 12 to 17 per cent in one, and in the other 6 to 14 per cent. They feel that indirect action has a bearing on this reduction, and they do not believe that the indications point decisively to the loss of a specific stimulus affecting the oxidative processes of the cells. It should be noted, however, that dog 1 of their series gained from an average weight of 8.11 kgm. before double oöphorectomy to an average weight of 8.69 kgm. after operation. This indicates a gain of 0.58 kgm. of fat, or an addition to the body weight of 7.1 per cent. Dog 2 of their series gained from an average weight of 10.89 kgm. before operation to the average weight of 11.48 kgm. after operation—an

[8] Durrant, E. P.: Studies on Vigor. (III). The Effect of Ovarian Extract Feeding on the Activity of Ovariectomized White Rats. *Endocrinology*, 1925, ix, 221.

[9] Hoskins, R. G.: Studies on Vigor. (II). The Effect of Castration on Voluntary Activity. *Amer. Jour. Physiol.*, 1925, lxxii, 325.

[10] Luethje, H., Über die Castration und ihre Folgen. *Arch. f. exp. Path. u. Pharm.*, 1902, xlviii, 184.

[11] Murlin, J. R., and Bailey, H.: Relation of the Sex Glands to Metabolism. *Surg., Gyn. and Obst.*, 1917, xxv, 332.

TABLE I

Patients not operated upon

AGE	MENSTRUATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL, RUSSELL SAGE STANDARDS	DATE OF BASAL METABOLISM	TREATMENT
	Third decade (still menstruating)				
29	Regular, normal	33	−10.9	March 30, 1921	
		35.3	−3.8	December 29, 1925	
		38	+4	May 6, 1926	
Average		35.4	−4.3		
	Fourth decade (patients still menstruating)				
37	Regular, normal up to recently, now sometimes every two weeks	39.3	+7.5	July 28, 1925	7–23–25. Nux vomica and gentian tonic
		42.1	+10.5	August 4, 1925	
39	Always irregular. No menses from September to December, 1924; also missed 2 months in Spring of 1925	40.5	+11	May 25, 1925	7–28–25. Luminal gr. ½ t.i.d.
		35.5	−2	August 4, 1925	
Average		39.3	+8		
	Fourth decade (patient after normal menopause)				
39	Regular, normal up to 1923; then missed 1–2–3 mos. at a time before it ceased finally in 1924	31.5	−13.5	July 23, 1925	
Average		31.5	−13.5		

Fifth decade (patients still menstruating)

41	Regular, normal. Decreased in amount Dec. 22, 1924; next period Feb. 8, 1925, March, June. Flushes for past 4 years	36.2	+0.5	February 21, 1925	2-17-25. K Br. Luminal
42	Regular, normal	34.1	−5.5	May 12, 1925	4-28-25. Salol
43	Regular, normal	35.2	−2	April 25, 1925	4-23-25. Nitroglycerine
44	Regular, normal up to birth of last child (6 yrs. ago) Since then 22–24 days' interval	36.7	+2.5	October 15, 1925	
44	Regular, normal up to August, 1925. Since then very irregular. Flushes for past year, now 3–4 daily	33.2	−7.5	October 17, 1925	10-17-25. {Nux vomica / Tr. digitalis} t.i.d.
		33.6	−7.25	December 17, 1925	12-1-25. Luminal gr. ½ t.i.d. 12-15-25 " gr. ss t. i.d.
45	Regular, normal. For past 2 years has menstruated twice a month (5–6 days). Flushes for 4–5 years	34.5	−4.5	April 1, 1925	3-24-25. Luminal gr. i ss q.n. 4-16-25. Cont. ℞.
46	Regular, normal up to last 2 years; since then 2–3 weeks' interval. Flushes twice weekly for past 2 years, not especially at menses	44.1 42.1	+22 +16.5	June 5, 1925 June 18, 1925	6-2-25. Bromide and Hyoscyamus mixture
46	Regular, normal. Missed one month (May, 1925) also June. Flushes in June	35.8	−0.5	July 23, 1925	
47	Regular, normal up to November, 1924. Every two weeks in November, December, January, February, March	39.5	+9.5	March 14, 1925	3-5-25- K Br. 3-12-25. K Br.

TABLE I—*Continued*

AGE	MENSTRUATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL. RUSSELL SAGE STANDARDS	DATE OF BASAL METABOLISM	TREATMENT
	Fifth decade (patients still menstruating)—Continued				
48	Regular, normal. For past two years has missed 2–3 months now and then	32.3	−10.5	April 11, 1925	
48	Regular, normal up to birth of last child (5 yrs. ago). Since then misses one month, sometimes two months. Many flushes after birth of last child. Better now	37.4	+4	April 19, 1925	4–8–25. Nux vomica and gentian tonic t.i.d. Na Br. gr. xx t.i.d.
49	Regular, normal, only once in two months since January, 1925	36	±0	January 6, 1926	
49	Irregular until marriage, regular since and normal until a year ago, 1924, when patient missed 4 months and then 3 months	31.2	−10.5	July 18, 1925	
49	Regular, normal up to past year, 2–3 months' interval now	28.4	−21.5	August 27, 1925	
Average		35.6	−1		
	Fifth decade (after normal menopause)				
43	Regular, normal. Ceased one year ago, returned in March (6 mos. later). None since	36.9	+3	October 29, 1925	10–21–25. Ward cough mixture at night. Luminal gr. ½ t.i.d.
46	Regular, normal up to 3 years ago; then every 2 months for one year when it stopped altogether	35.5	−1.5	March 31, 1925.	
Average		36.2	+1		

Average		36.2	+1		

Sixth decade (still menstruating)

50	Regular, normal. Intense headache. Missed 3 mos. one year ago	36.3	+2.5	December 1, 1925	
Average		36.3	+2.5		

Sixth decade (after normal menopause)

50	Regular, normal. Ceased 1920 or 1921	27.9	−20	May 25, 1925	
50	Regular, normal. Ceased in January, 1925, suddenly. Since then legs get numb from knees downward	35.9	+3	May 26, 1925	5–20–25. Bromide and hyoscyamus mixture
50	Always irregular since typhoid 28 yrs. ago. Missed one month, then menstruated twice in month. About 5 yrs. ago began to miss 1–2 mos. regularly. Ceased altogether 2 yrs. ago until September, 1924. None since	36.2	+3.5	June 13, 1925	
51	Regular, normal. Missed October 1923 and March, 1924. None since. Flushes, 6–7 daily, since Fall of 1924	28.7	−18.5	February 28, 1925	2–10–25. K Br. gr. xv q.n.
51	Regular, normal. Ceased after influenza in 1918. Flushes at times periods should appear	39.4	−15	May 11, 1925	5–5–25. Sod. Brom. gr. x t.i.d.p.c. 5–7–25. Cont. B.
51	Regular, normal until 16 years ago; then every 21 days. Since two years ago every two weeks. Missed May, 1924, and ceased after June, 1924	31.7	−11	March 30, 1925	2–17–25. K Br. gr. xv q.n. 3–26–25. Luminal gr. i ss q.n. Nitroglycerine p.r.n.
52	Regular, 5–20 days. Ceased gradually, last period 1923	32.7	−7	March 28, 1925	

TABLE I—*Concluded*

AGE	MENSTRUATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL, RUSSELL SAGE STANDARDS	DATE OF BASAL METABOLISM	TREATMENT
	Sixth decade (after normal menopause)—Continued				
53	Regular, normal. Ceased gradually with skipping of single period. Last period May, 1924	34.9	−1	November 19, 1925	
54	Irregular, scant. Ceased in 1923. Headaches monthly since; also flushes and dizziness	32.3 34.9	−8 ±0	April 15, 1925 October 7, 1925	4-14-25. Luminal gr. i $\overline{ss}$ q.d.
55	Regular, normal except for very severe pain. After birth of children (19–24 years ago) irregular, sometimes interval of 9 weeks. Very much pain always. Cessation gradual, intervals of two to three months Last period in 1919	35.6	+1.5	August 20, 1925	8-18-25. Kl and Gout mixture
56	Regular, normal. Ceased October, 1922. Flushes before menopause, none since. Cold sweats now...	36.5	+4.5	March 25, 1925	2-12-25 K Br. gr. xv. b.i.d. for 3 days then q.d. Aspirin p.r.n.
Average		33.9	−3		

average gain of 5.4 per cent. The authors noted correctly that the relative increase in weight is less than the relative reduction in metabolism.

To throw more light on this complex subject further experiments with animals are necessary.

Very important observations upon women come from German sources. Kraul and Halter[12] studied the basal metabolism in five women in whom amenorrhoea had been produced by the Roentgen ray. They reported a reduction of metabolism in each case, amounting to from 17 to 30 per cent. Plaut and Timm[13] carried on similar work, producing amenorrhoea by the Roentgen ray over the ovaries. The basal metabolism of their patients fell 100 to 300 calories a day, the fall beginning at the onset of amenorrhoea. After several months the metabolism returned spontaneously to normal. They feel that this subsequent rise is to be attributed to compensatory thyroid hyperfunction and, furthermore, that such thyroid hyperfunction may explain the symptoms of the menopause. Zuntz[14] studied four women before and after castration, following three of them through a period of oöphorin treatment. The oxygen consumption per kilo per minute of the four women averaged 4.7 cc. before operation; three to six weeks after operation it was 4.63 cc. Seven weeks to fifteen months after operation it was 4.4 cc. in three cases followed. In the same three cases, ovarian tablets had no effect upon the metabolism; hence the author questioned the results of Loewy and Richter.[6] In view of the fact that two of Zuntz's cases suffered from tubo-ovarian abscess, one from tubal pregnancy, one from tumor of the ovary, the fall in oxygen absorption after operation is hardly significant.

Korenchevsky[15] makes the interesting differentiation of eunuchs into

[12] Kraul, L., and Halter, G.: Die Beziehungen der weiblichen Genitalien zum Grundumsatz. *Ztschr. f. Geburtsh. u. Gyn.*, 1924, lxxxvii, 606.

[13] Plaut, R., and Timm, H. A.: Ueber den Einfluss der Keimdrüsen auf den Stoffwechsel. *Klin. Wchnschr.* (Berl.), 1924, iii, 1664.

[14] Zuntz, L.: Experimentelle Untersuchungen über den Einfluss der Kastration und der Oöphorindarreichung auf den Stoffwechsel der Frau. *Ztschr. f. Geburtsh. u. Gynaek.*, 1904, liii, 352.

[15] Korenchevsky, V.: The Sexual Glands and Metabolism. (I). Influence of Castration on Nitrogen and Gaseous Metabolism. *Brit. Jour. Exper. Path.* (Lond.), 1925, vi, 21.

TABLE II

Patients operated upon

AGE	DIAGNOSIS OF DISEASES	OPERATIONS AND DATES	INTERVAL BETWEEN OPERATION AND EXAMINATION	MENSTRUAL HISTORY BEFORE OPERATION	MENSTRUAL HISTORY AFTER OPERATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL. RUSSELL SAGE STANDARDS	DATE	TREATMENT
			Third decade						
20	Chronic Pelvic Inflammatory Disease. 2–18–22	Bilateral salpingectomy. Left oöphorectomy. Appendectomy. Modified Coffey suspension of Uterus 2–28–22	3 yrs. 10 mos.	Regular, every month	Very bad pain for one day each month since operation; also one flush weekly. Menstruation regular, natural	31.1 33.2	−17 −10.75	December 28, 1925 January 19, 1926	1–5–26. "Brown liquid," probably nothing to affect B.M.
20	Eczema Erythematosum Crustosum. 4–25–19.	Double salpingectomy Right oöphorectomy } 8–2–21 Appendectomy	4 yrs. 5 mos.	Regular, every month	No change	36.3	−3.7	December 28, 1925	
22	Obesity Syphilis } 7–7–25	Bilateral Salpingo-oöphorectomy, 11–4–23	1 yr. 9 mos.	Regular up to marriage; very irregular afterwards. Sometimes twice monthly	3–4 flushes daily after operation, erythema. None for past 3 months. Menses ceased with operation	34.8	−6	July 7, 1925	
26	Dysmenorrhoea. 6–17–18 Laceration of Cervix. 7–17–18 Splanchnoptosis Pelvic Infection } 7–18–21	Bilateral Salpingectomy Rt. oöphorectomy Appendectomy 11–4–22	2 yrs. 8 mos.	Regular	Irregular, ahead of time, lasting 8 days to 2 weeks	41	+11	June 25, 1925	6–11–25. Nux vomica and Gentian tonic t.i.d.

28	Hyperopia. 1-23-11 Hordeolum. 9-12-15 Retroposition uterus Ovarian Cyst, left; 4-1-22 Chronic Appendicitis	Tonsillectomy. 1913 Left salpingo-oöphorectomy Rt. Salpingectomy Modified Coffey Suspension of Uterus. Appendectomy. D. & C. 9-21-22	3 yrs. 3 mos.	Regular, normal, of 3 days' duration.	Now lasts 5 days, ceases after 2 days then returns. Very much pain	36.6	−1	December 31, 1925	
29	No medical disease	Right oöphorectomy, 1920	5 yrs.	Regular, profuse	Ceased with last operation.	34	−8	November 24, 1925	6-17-26. Luminal gr. 1½ q.d.
		Left oöphorectomy. 1922	3 yrs.		Flushes since then, several daily now. Sick in bed every two weeks with headache and vomiting	38.3	+3.5	June 22, 1926	
Averages: Double oöphotectomy						35.7	−3.5		
Unilateral oöphorectomy						35.64	−3.7		
				Fourth decade					
30	Ureteral Stricture, left, 5-20-25	Bilateral Salpingectomy Left oöphorectomy Modified Coffey Suspension of uterus Appendectomy 10-2-23	2 yrs. 3 mos.	Irregular, every 6-8 weeks	Regular, every 4 weeks. Flushes for a year after operation, disappeared recently	35.9	−1.75	December 31, 1925	
30	Salpingitis, chronic, bilateral Hydrosalpinx, right Peri-appendicitis, chronic Syphilis (Wassermann) 12-29-22	Bilateral Salpingectomy Modified Coffey Suspension of Uterus. Right oöphorectomy Appendectomy 12-30-22	3 yrs.	Regular, normal	No symptoms. Cramps for one day after menstruation, always	38.4	+4.7	December 28, 1925	

TABLE II—*Continued*

AGE	DIAGNOSIS OF DISEASES	OPERATIONS AND DATES	INTERVAL BETWEEN OPERATION AND EXAMINATION	MENSTRUAL HISTORY BEFORE OPERATION	MENSTRUAL HISTORY AFTER OPERATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL, RUSSELL SAGE STANDARDS	DATE	TREATMENT
			Fourth decade—Continued						
30	Hysteria, 8–11–25 Middle ear deafness on left side, slight, 8–11–25	Panhysterectomy. 1918–1921	5 yrs.	Always irregular, 10 days to 6 weeks, always painful with headaches	Ceased with operation. Flushes daily since operation	36.9	±0	August 13, 1925	
31	No medical disease	Right salpingo-oöphorectomy 1921	4 yrs.	Regular, normal	No change	32.4	−11	April 29, 1925	
32	No medical disease	Hysterectomy. Double oöphorectomy Appendectomy 10–16–22 Anterior Colpotomy. 11–8–22	3 yrs. 2 mos.	Regular, normal	Ceased with operation. Many flushes daily for 2–3 days at times periods should appear, also vertigo and dizziness	39.3	+8	December 30, 1925	
32	No medical disease	Double oöphorectomy Appendectomy 2–6–24	1 year	Regular up to marriage, Since has often missed two months. Headaches, much pain	Ceased with operation. Extreme headaches, weakness, vomiting with loss of power in legs, and flushes—all since operation but at no regular intervals	37.03 36.8 38.25	+2 ±0 +4.5	February 14, 1925 February 25, 1925 October 22, 1925	2–5–25. K Br. gr. xv, q.n. 3–10–25. K Br. gr. xv, q.n. also pyramidon when necessary

33	Obesity—7-10-23 Infectious Arthritis of Left Sacroiliac. 6-25-25	Hysterectomy. Double Salpingectomy. Left oöphorectomy Appendectomy 12-4-23	1 yr. 6 mos.	Regular, normal	Slight sign every month since operation—for 3 days Dull feeling in head, and flushes	34.1	−6.5	June 8, 1925	
37	Cystic ovary Post-operative adhesions, 5-30-20	Appendectomy and part of one ovary, 1915 Hysterectomy. Right oöphorectomy. June, 1920	9 yrs. 4 yrs. 6 mos.	Irregular, severe pain, 8-10 days Ceased 13 months before last operation	Ceased before last operation. Severe headaches lasting 4-5 days, nausea, vomiting, twice monthly. Vertigo causing pt. to lose consciousness and to fall. Flushes beginning one year after operation	36.5	±0	December 9, 1924	
37	Tubo-ovarian abscess, right, 4-8-22	Rt. Salpingo-oöphorectomy. 4-8-22	2 yrs. 3 mos.	Regular. Always much pain, in bed for one day	Continues as before	33.6	−8.5	June 2, 1925	
37	Eczema Intertrigo. 8-14-19 Chronic Tonsillitis Oral Sepsis 4-18-21 Adenoids, slight Psychoneurosis. 1-24-22	Appendectomy. 1915 Hysterectomy Left salpingo-oöphorectomy Right salpingectomy 12-20-17	7 yrs.	Regular, normal	Ceased with operation. Headaches and feels ill 3 days every month	35.8	+0.6	January 18, 1922	
39	Hypertension $\left(\frac{190}{118}\right)$ Obesity (212 lbs.) 3-16-26	Hysterectomy. Salpingo-oöphorectomy—right; excision of umbilicus 4-30-24	2 yrs.	Irregular. 3-4 weeks, lasting 4-10 days, much pain in knees	Ceased with operation. For last few months, headaches dizziness, and flushes followed by cold	38.9	+7	March 18, 1926	
Averages: Double oöphorectomy Unilateral oöphorectomy						37.5 35.7	+2.7 −2.2		

TABLE II—*Continued*

AGE	DIAGNOSIS OF DISEASES	OPERATIONS AND DATES	INTERVAL BETWEEN OPERATION AND EXAMINATION	MENSTRUAL HISTORY BEFORE OPERATION	MENSTRUAL HISTORY AFTER OPERATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL. RUSSELL SAGE STANDARDS	DATE	TREATMENT
			Fifth decade						
41	No medical disease	Appendectomy. Ligation of both tubes Ventral fixation of the Uterus Repair Relaxed Vaginal Outlet 3-25-08 Hysterectomy. Release of Adhesions. Repair Relaxed Vaginal Outlet, 6-7-22	2 yrs. 11 mos.	Regular, 10–12 days, profuse	Ceased with operation. Flushes and headaches every month for 2 years after operation	37.4	+3	May 7, 1925	
42	Hypertension. $\frac{198}{122}$ 11-27-25	Cauterization of Cervix Anterior Colpoperineorrhaphy 5-23-23 Drainage of Pelvic Abscess Sept. 1 and 8, 1923 Post. Colpotomy. 11-20-23 Posterior Colotomy with drainage. Hysterectomy. Double Salpingo-oöphorectomy 1-15-24	1 year	Regular, much pain	Ceased with operation. Giddiness, flushed, prostration, headaches for 2-3 days every month since operation	41.76 38.1	+16.5 +5	February 18, 1925 May 28, 1925	2-10-25. K Br. gr. xxx for 3 n. then gr. xv q. n 2-24-25 K Br. xv q.n. 3-19-25. Disc. K Br. Luminal 5-7-25 K Br. gr. xv bd for 3 days, then q. d.
43	Ovarian Cyst (Rt). 6-17-07 Ovarian Cyst. 5-31-21	D. & C. Release of Pelvic Adhesions. Ventral Suspension of Uterus Appendectomy 6-23-07 Hysterectomy. Double Salpingo-oöphorectomy 6-8-21	4 yrs.	Regular, normal, 7 days	Ceased with operation. Irritable, headaches every month since operation	42.1	+16.75	November 3, 1925	10-15-25. Nux vomica and Gentian Tonic t.i.d.

44	Retroposition Uterus Ovarian Cyst, left Chronic Appendicitis } 4-1-22	Hysterectomy. Left Salpingo-oöphorectomy Appendectomy 4-4-22	3 yrs. 8 mos.	Regular, normal up to 17 years ago, then every 2 weeks	Ceased with operation. No monthly symptoms. No flushes but nervous chills which awaken patient at night	34.6	−4	December 31, 1925	
45	Lumbo-sacral strain. 1-29-25 Obesity. 1-29-25	Separation of Adhesions 1897 Hysterectomy. Bilateral Salpingo-oöphorectomy January 1921	4 yrs.	Regular, normal	Ceased with operation. No monthly symptoms. Dizziness since operation and flushes, 4-6 daily at first, now not quite every day	36.5	+1.5	March 10, 1925	3-9-25. Aspirin gr. x t.i.d. p. c. today
47	Infectious Arthritis of Spine (?) 1-28-26 (Probably no significant disease)	Oöphorectomy. 1913 Oöphorectomy. 1914	13 yrs. 12 yrs.	Regular, normal except for pain which kept patient in bed 2 days	Ceased with second operation	31.64	−12	April 27, 1926	
47	Lumbo-Sacral strain. 2-3-25	Hysteromyomectomy. Appendectomy 11-5-19	5 yrs. 5 mos.	Regular, normal	Ceased with operation. No monthly symptoms. Flushes since operation, nightly and very severe, now once weekly	33.6	−7	April 29, 1925	
48	No medical disease	Hysterectomy. Bilateral Salpingo-oöphorectomy Appendectomy 1-5-22	3 yrs. 5 mos.	Regular, normal	Ceased with operation	32.15	−11	May 25, 1925	

TABLE II—*Concluded*

AGE	DIAGNOSIS OF DISEASES	OPERATIONS AND DATES	INTERVAL BETWEEN OPERATION AND EXAMINATION	MENSTRUAL HISTORY BEFORE OPERATION	MENSTRUAL HISTORY AFTER OPERATION	CALORIES PER SQUARE METRE PER HOUR	DEVIATION FROM NORMAL. RUSSELL SAGE STANDARDS	DATE	TREATMENT
			Fifth decade—Continued						
49	Pelvic Inflammatory Disease 2–20–29 Arterio-Sclerosis, Hypertension 6–29–25	Vaginal Puncture. 2–20–99 D. & C. 2–24–04 Left Salpingo-oöphorectomy, Right Salpingectomy, Resection Right Ovary, Appendectomy 5–20–12 Hysterectomy. Release of Adhesions. Intestinal Resection. Intestinal Anastomosis. Radical Cure of Ventral Hernia 3–26–17	12 yrs. 10 mos. 7 yrs. 3 mos.	Regular, normal	Ceased after operation. 1917. Flushes since then, very many at first, not so many now, still some daily	36.1	+0.5	July 6, 1925	
Averages:									
Double oöphorectomy						37.04	+2.8		
Unilateral oöphorectomy						35.35	−1.8		
Hysterectomy alone						35.50	−1.4		
			Sixth decade						
53	Sub-acute Salpingitis 1–11–23	Hysterectomy Bilateral Salpingo-oöphorectomy 1–13–23	1 yr. 11 mos.	Irregular, profuse	Ceased with operation. Flushes daily after operation, now very occasional	31.7	−9.4	April 14, 1925	4–7–25. K Br. gr. xv q.n.

57	Oral Sepsis. 3-26-23	Appendectomy Suspension of Uterus 1904 Supra-Vaginal Hysterectomy. 4-12-19	5 yrs. 11 mos.	Regular, normal	Last period April, after operation. Flushes frequently, at irregular intervals since operation	33.5	−5	May 21, 1925	
Summary:									
Double oöphorectomy						31.7	−9.4		
Hysterectomy alone						33.5	−4.3		
Seventh decade									
65	Arterio-Sclerosis 7-24-24	Hystero-Salpingo-oöphorectomy 1-9-02	23 yrs. 3 mos.	Regular, normal, 3 weeks early before operation	Ceased with operation	31.76	−6.6	April 13, 1925	4-9-25. Nux vomica and Gentian Tonic t.i.d.
Summary:									
Double oöphorectomy						31.76	−6.6		

the fat and the thin varieties. Fat castrated dogs seem to show a fall of basal metabolism, thin ones no change or even an increase in metabolic rate.

It is obvious, therefore, that the present experimental and clinical evidence regarding the effect of ovariectomy upon the basal metabolism is highly contradictory. This contradiction becomes apparent when one considers the impression gathered from the literature by DuBois, on the one hand, and by Aub and by Bailey on the other.

There is a rather striking lack of human data bearing upon the subject. This is unfortunate because human beings are the most coöperative subjects for the study of basal metabolism. One practical difficulty is that normal women do not undergo bilateral oöphorectomy: pelvic abscess, probably the most common cause for the opera-

TABLE III

Table showing the deviation per cent of the basal metabolism of the various groups here studied from the Russell Sage Standards of normal

AGE	NORMAL CONTROLS		BILATERAL OÖPHORECTOMY		PARTIAL OÖPHORECTOMY		HYSTERECTOMY ALONE	
	Number studied	Per cent deviation	Number studied	Per cent deviation	Number studied	Per cent deviation	Number studied	Per cent deviation
20–30	1	−4.3	2	−3.5	4	−3.7	0	
30–40	3	+3.5	3	+2.7	8	−2.2	0	
40–50	16	−0.83	5	+2.8	2	−1.8	2	−1.4
50–60	12	−2.6	1	−9.4	0		1	−4.3
60–70	0		1	−6.6	0		0	

tion, precludes the proper determination of the metabolic rate before operation. It has been impracticable for me to follow the basal metabolic rate of a given patient from a pre-operative determination over a period of some months after operation, which would be an interesting observation.

However, it is possible to determine accurately whether or not there may be any lasting reduction of basal metabolism following oöphorectomy by the comparison of results obtained upon women upon whom the operation has been done with those from normal women of corresponding ages. It seemed to me a valuable check to make comparisons of the results not only with usual normal standards (Aub and

TABLE IV

Table of pre-operative and post-operative net weights

PRE-OPERATIVE WEIGHTS	OPERATION	POST-OPERATIVE WEIGHTS	INTERVAL FOLLOWING OPERATION
	Operations involving the removal of both ovaries		
	Age 20–30		
pounds		*pounds*	
117	Bilateral salpingo-oöphorectomy	145	1 yr. 9 mos.
112	Bilateral oöphorectomy	124	4 yrs.
	Age 30–40		
128	Bilateral oöphorectomy	150	1 yr. 2 mos.
126	Hysterectomy and bilateral oöphorectomy	134	3 yrs. 2 mos.
161	Hysterectomy and bilateral oöphorectomy	111½	4 yrs.
	Age 40–50		
131	Hysterectomy and bilateral salpingo-oöphorectomy	190	1 yr. 4 mos.
117	Hysterectomy and bilateral salpingo-oöphorectomy	142½	3 yrs. 4 mos.
176	Hysterectomy and bilateral salpingo-oöphorectomy	220	4 yrs. 2 mos.
140	Hysterectomy and bilateral salpingo-oöphorectomy	142	4 yrs. 5 mos.
168*	Bilateral-oöphorectomy	144	12 yrs.
	Age 50–60		
118	Hysterectomy and bilateral salpingo-oöphorectomy	146	2 yrs. 3 mos.
	Age 60–70		
Unknown	Hysterectomy and bilateral salpingo-oöphorectomy	100	23 yrs.
	Operations involving removal of one or of one and a fraction ovaries		
	Age 20–30		
113	Bilateral salpingectomy. R. oöphorectomy	134	2 yrs. 8 mos.
96	L. salpingo-oöphorectomy. R. salpingectomy	97	3 yrs. 3 mos.
119	Bilateral salpingectomy. L. oöphorectomy	159½	3 yrs. 11 mos.
Unknown	Bilateral salpingectomy. R. oöphorectomy	139	4 yrs.

TABLE IV—*Continued*

PRE-OPERATIVE WEIGHTS	OPERATION	POST-OPERATIVE WEIGHTS	INTERVAL FOLLOWING OPERATION
	Age 30–40		
pounds		*pounds*	
180	Hysterectomy. Bilateral salpingectomy. L. oöphorectomy	179	1 yr. 6 mos.
208	Hysterectomy. R. salpingo-oöphorectomy	212	1 yr. 11 mos.
108	Bilateral salpingectomy. L. oöphorectomy	126	2 yrs. 2 mos.
116	Bilateral salpingectomy. R. oöphorectomy	101	3 yrs.
121	R. Salpingo-oöphorectomy	177	3 yrs. 2 mos.
157	R. Salpingo-oöphorectomy	177	5 yrs.
136	Hysterectomy. L. oöphorectomy. Bilateral salpingectomy	173	7 yrs. 2 mos.
136	Removal of part of one ovary. Hysterectomy. R. oöphorectomy	165	9 yrs. 4 yrs.
	Age 40–50		
116	Hysterectomy. L. salpingo-oöphorectomy	135	2 yrs. 8 mos.
176	Bilateral salpingectomy		13 yrs.
	L. oöphorectomy. Resection of R. ovary. Hysterectomy	148½	7 yrs.
	Operations involving hysterectomy alone		
	Age 40–50		
188	Hysterectomy	198	2 yrs. 11 mos.
143	Hysterectomy	159	5 yrs. 5 mos.
	Age 50–60		
124	Hysterectomy	143	6 yrs. 1 mo.

* Maximum before and after operations, 1913–1914.

DuBois), but also with results obtained from a number of normal women examined under identical conditions, by the same operator, using the same apparatus. The results of such comparisons are seen in the table.

While dispensary patients may not seem at first thought to be ideal controls, yet it is possible to have much more careful general and special examinations in the hospital than could be carried out upon subjects obtained in a casual way from among supposedly healthy persons. I am satisfied from a perusal of the records of the women

not operated upon of their essential normality, particularly as concerns their metabolic rate.

I feel that I can obtain more consistently good results in routine work by the method of carbon-dioxide collection, the application of which to basal metabolism determination has been described.[16,17,18] For the work reported here, however, we have used the closed method of oxygen absorption. This was done because the CO_2 collection apparatus is not sold, and is not in so wide use as are the various types of O_2 absorption apparatus, and it was thought desirable to obtain results by a method that is in wide use in order to facilitate the interpretation of results.

It is obvious that neither bilateral nor partial oöphorectomy, nor hysterectomy alone causes any permanent alteration in the basal metabolism. The only possible significant alteration is in the case of double oöphorectomy in the sixth decade, but as this figure (−9.4 per cent) is derived from only one case, it may be dismissed as of no importance.

THE EFFECT OF THE OPERATIONS UPON BODY-WEIGHT

A table is shown comparing the body-weights of patients before and after the three types of operation.[19] Since a change of weight causes a change in body surface, one square meter of which is the unit for the expression of the basal metabolism, it is important to know whether such an alteration in body surface takes place after operation or not. It is also very interesting to show whether or not a considerable deposit of fat, which is relatively inert as regards its relation to metabolism, is accompanied by a proportionate increase in basal metabolism.

[16] King, J. T., Jr. with a Statistical Note by Raymond Pearl: Determination of the Basal Metabolism from the Carbon-Dioxide Elimination. *Johns Hopkins Hosp. Bull.*, 1921, xxxii, 1.

[17] King, J. T., Jr.: The Gas Exchange in Diseases of the Thyroid Gland. *Ibidem*, 1923, xxxiv, 304.

[18] King, J. T., Jr., and Cross, V. B.: Superventilation and Carbon-Dioxide Elimination. *Ibidem*, 1923, xxxiv, 349.

[19] All post-operative weights are from our own records. Most pre-operative weights are from the patients' statements: the pre-operative weights contained in the table are probably substantially correct.

Briefly, the effect of bilateral oöphorectomy was as follows: 9 of the 12 patients showed a substantial gain in weight, averaging 25.4 pounds; 2 patients lost heavily, on an average 34.3 pounds. In one case the pre-operative weight was not known.

Of 13 patients from whom one ovary or one and a part of the other ovary were removed, 10 showed substantial gains in weight—averaging 24.6 pounds. In 3 cases there was an average loss of 14.5 pounds.

Hysterectomy was followed in 2 cases by an average gain of 13 pounds, in 1 case by a loss of 19 pounds.

DISCUSSION

While one cannot say from the results shown above that the basal metabolism is never affected by radical pelvic operations, it can be said with safety that, if such a change in basal metabolism does occur, it must be very rare. In other words, if a patient who has had such a pelvic operation is found to have a reduction in basal metabolism, we should not throw the responsibility upon the operation without due consideration of the possibility of a coincidence of the two conditions.

The normality of basal metabolism following bilateral or unilateral oöphorectomy is emphasized by the gain in weight. It seems that an increase in total basal metabolism goes *pari passu* with the increase in body surface due to the deposition of fat. It is very interesting to consider that this occurs, since the "active protoplasmic mass" (Benedict), which causes most of the heat production of the body, must have been little changed following operation. In other words, the basal metabolism in these cases follows the body surface rather than the "active protoplasmic mass."

In all these considerations, however, we must remember that our weights and our basal metabolism determinations were taken some time after the operations, though all but four observations were made within 5 years. We have not ruled out the possibility of the existence of a temporary period after oöphorectomy during which the basal metabolism may be reduced. From our results, it seems that such a phase, if there be such, does not last as long as a year.

The time of our observations must be considered also in relation to the observed fact that the metabolism per unit of body surface remains unchanged by substantial gains in weight. In Benedict's

well known starvation experiment the basal metabolism did not fall in proportion to the body surface. I have followed the basal metabolism in a few instances in which substantial gains in weight occurred over a short period of time and the basal metabolism did not rise in proportion to the increased body surface. It is likely that stimulation or depression of the active protoplasmic mass does not follow immediately upon rapid changes in the fat reserve of the body. Our figures show clearly, however, that the heat production per unit of body surface is quite normal following the deposition of fat when the observations are made one year or more after the operations that cause such fat deposits.

CONCLUSIONS

1. Pelvic operations upon women (bilateral oöphorectomy, unilateral oöphorectomy, hysterectomy) were found to cause no permanent change in the basal metabolism.

2. The basal metabolism following such operations does not differ significantly from either the Sage Institute Standards nor from figures taken by us from normal women under conditions identical with those under which the patients who had been operated upon were studied.

3. Our observations upon normal women support the Sage Institute Standards in all groups which include a number of observations sufficient to be of significance.

4. There is a tendency to a substantial gain in weight in most cases after complete or partial oöphorectomy.

5. Increase of body surface from deposition of fat is associated with a proportionate increase in basal metabolism.

6. Deposition of fat after oöphorectomy is not due to alteration of basal metabolism. It is probably due to reduced vigor.

THE SIGNIFICANCE OF GASTRIC ANACIDITY[1]

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INTRODUCTION

Ever since the introduction of methods of gastric analysis physicians have noted that certain people who apparently have no serious anatomical disease of the stomach fail to secrete hydrochloric acid after the ingestion of a test-meal. In the attempt to explain this apparent anomaly a great many observations have been put on record, and a huge literature has accumulated in which various theories are set forth and in which the possible relationship of gastric anacidity to one or another morbid condition is suggested. A review of the bibliography is beyond the scope of this paper, but the main views which have been held may be briefly summarized.

It has been known for many years that so-called pernicious anemia is nearly always, if not invariably, associated with gastric anacidity, and since autopsies in this disease reveal an atrophy of the gastric glands, it was not illogical to conclude that an anatomical lesion (gastritis) was present in all cases of achlorhydria. A gastritis undoubtedly does account for a good many instances of deficient acid secretion, but few if any observers now regard it as a satisfactory explanation for all cases, inasmuch as many people with anacidity live for years in good health and without digestive symptoms. Martius (1), going, to the other extreme, has upheld the opinion that gastric achlorhydria in certain people is a constitutional anomaly, congenital and perhaps hereditary. The frequency of the condition in individuals without symptoms or other signs of gastric disease is stressed in support of this theory, which has, however, been vigorously combated by Faber (2) and his associates. Faber believes that even in the cases in which there is no evidence of outspoken anatomical lesion a "toxin," developed in some other part of the body, disturbs the function of the

[1] Submitted for publication August 1, 1926.

gastric glands. The supposed occurrence of transient anacidity in severe fevers, in intestinal disturbances, in nephritis and in other disorders is adduced in support for this view. Many writers have regarded anacidity rather indefinitely as a "neurosis," pointing out its occurrence in "neurotic" individuals, but this explanation is obviously unsatisfactory. Finally, the condition has been causally associated by one writer or another with almost every disorder, defect, and ailment to which the human body is subject. To select only a few items from this long list one may mention gall-stones, gastric ulcer, dental disturbances, "focal infections," asthma, acne rosacea, hyperthyroidism, "infectious" arthritis, tuberculosis and syphilis.

In summary, then, the general implication from the literature is to the effect that gastric anacidity is usually "brought on" by some definite disorder in or remote from the stomach, and that if such disorder can be corrected, the secretion is likely to be reëstablished. The causal relation of digestive or other symptoms to anacidity is an interesting chapter on which not enough critical observations are on record to warrant discussion.

The purpose of the present communication is two-fold: in the first place, to present a critical analysis of a large number of instances of gastric anacidity detected during the course of routine gastric analysis in patients coming to a general medical clinic, and not presenting themselves primarily because of digestive symptoms, and in the second place, to expose the quantitative relations between volume of secretion, acidity and motility in a smaller group studied by the methods previously described by us (3)[2] with a view to a possible better understanding of the disorder.

ANACIDITY IN NORMAL PEOPLE

Several recent careful studies of the reaction of the stomach contents of infants are of importance. Marriott and Davidson (4) aspirated

[2] We should like to call attention to a typographical error in our paper which appeared in the *Arch. Int. Med.*, **37,** 819 (June) 1926. On page 822, under (6) the formula (1) should be $\left(\frac{x}{y} \times a\right) - a$ equals the maximum possible amount of juice secreted in ten-minute period, instead of $\left(\frac{y}{x} \times a\right) - a$ equals the maximum possible amount of juice *excreted* in a ten-minute period.

the stomach two hours after feeding. In the case of 41 normal infants only ten specimens had a pH of 3.0 or lower. The lowest value was pH 2.0 and the majority fell between pH 3.0 and pH 5.0. Davison (5) criticized the previous work on the grounds that saliva and regurgitated duodenal contents might mask the true acidity of the gastric contents. However, he too found that in 18 specimens obtained from normal infants and free from amylase and trypsin the pH varied between 3.6 to 5.5. Inasmuch as the gastric juice of normal adults usually has a pH of approximately 1.2 to 1.4, it is clear that in these infants the stomach contents were ten-fold to several thousand-fold less acid. It is possible, therefore, that the activity of the gastric glands is not fully developed until some time after birth, a point which perhaps is in harmony with the view of Martius to which we have referred above. In this connection one may also refer to the fact emphasized by Carlson (6) that pepsin and HCl are absent in the invertebrates and that "it would seem that gastric juice is a comparatively late addition to the animal digestive processes."

With regard to normal adults we shall refer to only a few of the more recent studies which have been carried out with particular care. Bennett and Ryle (7) examined 100 apparently perfectly normal, healthy young adults, using the fractional gruel meal. In four of them no free HCl, as determined by di-methyl, appeared during the test. Baird, Campbell and Hern (8) later found two instances of anacidity among a similar group of 57 people. There was no definite correlation between the degree of acid secretion and physical fitness. In another group of 60 normal people, Bennett (9) found HCl absent at the end of an hour in two cases. It appears therefore that even among groups of "supernormal" people approximately one in twenty has a deficient gastric secretion. In more miscellaneous groups the figures in the literature run somewhat higher, and among the clients of the gastro-enterologist, a considerable proportion of whom, of course, have serious anatomical disease of the stomach, the number rises to approximately 20 per cent.

PART I. STATISTICAL OBSERVATIONS ON GASTRIC ANACIDITY

The present observations are based on a study of 1500 consecutive gastric analyses made on patients entering the general medical wards

of the Johns Hopkins Hospital. The diagnosis was based in each case on the absence of free HCl (as tested by di-methyl) in the gastric contents, 45 minutes to 1 hour after ingestion of the Ewald meal. There was no special selection of material and in most cases the gastric analysis was done as part of a general diagnostic study and not because the patient complained of digestive disturbances.

The material may be divided into several groups: (1) Patients with digestive disorders; (2) Those with diseases of various sorts not primarily of the digestive tract; (3) Patients in whom careful study revealed no evidence of any anatomical disease.

There were 153 diagnoses in the 1500 patients, of whom 780 were males and 720 females. The ages varied from 10 to 81 years.

Among the total of 1500 people there were 390 instances of anacidity, or 26 per cent, and if one eliminates the patients with known disease of the stomach, such as carcinoma and so-called pernicious anemia, the percentage of anacidities among the remainder falls to 20 per cent.

In an attempt to find out to what extent the various factors which are supposed to influence gastric secretion played a part in the present group the series has been analysed from various points of view.

The relation of age to gastric acidity apart from disease of the stomach

It has been found by many observers that gastric anacidity seems to increase in frequency as groups of older people are examined. For example, Dedichen (10) found gastric anacidity in 66 per cent of 99 patients between the ages of 67 and 92 years, and it should be emphasized that these examinations were done on healthy old people. On the other hand, Bell (11) states that, in a series of patients studied by him, hyperchlorhydria was more common over than under 40 years of age, and he concluded that these observations disproved the assumption that gastric acidity decreased with advancing age. However, if one examines his tables, they show very clearly that the percentage of patients with anacidity gradually increased with age.

In Chart 1 the frequency of anacidity in relation to age is shown graphically (1) in the entire group of 1500 cases (2) in the entire group, excepting those with disease of the stomach and (3) in the group without any evidence of anatomical disease. It is obvious that the fre-

quency of anacidity increases with advancing years and that the incidence in the three groups is quite similar. In alleging any disease as a cause of anacidity, therefore, the age incidence must be taken into account. For example, one would clearly expect to find anacidity more frequently in arteriosclerosis, a disorder of old people, than in healthy young adults, but this does not necessarily mean that arteriosclerosis is a cause of anacidity unless there is a significant deviation from the normal curve of age incidence. This point will be dealt with more fully below.

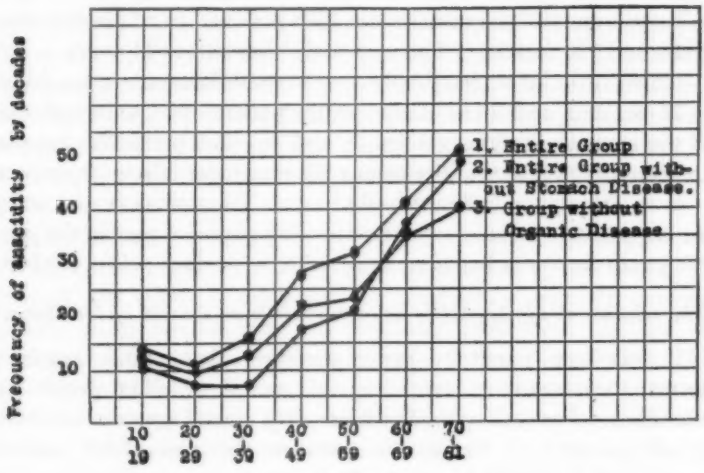


CHART 1

Influence of disease on gastric acidity

I. Anacidity in patients with diseases of the stomach. In column A of Chart 2, we have indicated the percentage of cases of anacidity in different disorders in which the stomach is the site of disease. There are 178 examples, including carcinoma, so-called pernicious anemia, gastritis (alcoholic, mercurial, and gastritis associated with hepatic cirrhosis) and gastric ulcer. In each instance, except in the ulcer cases, the incidence of anacidity is over 40 per cent.

II. Anacidity in patients without organic disease. The frequency of anacidity in patients without any demonstrable organic disease is

indicated in column B of Chart 2. There were 570 persons in this group. The gastric analyses were done as a part of a routine diagnostic procedure. The diagnoses included psychoneurosis, neurasthenia,

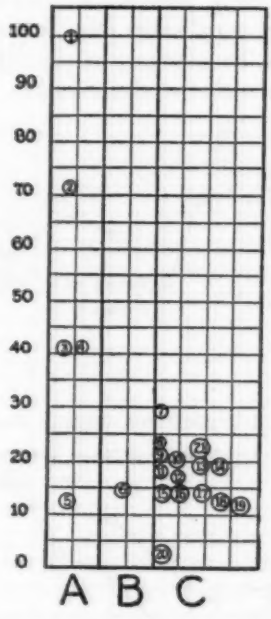


CHART 2. Group A: 1, pernicious anemia; 2, carcinoma of stomach; 3, gastritis, alcoholic and mercurial; 4, gastritis, associated hepatic cirrhosis; 5, peptic ulcer.

Group B: 6, group without organic disease.

Group C: 7, hyperthyroidism; 8, carcinoma other than carcinoma of the stomach; 9, disease of lungs; 10, gall-bladder disease; 11, arthritis; 12, diseases of the intestinal tract; 13, chronic infections; 14, syphilis; 15, disease of the heart; 16, disease of the kidney and blood vessels; 17, disease of the nervous system; 18, chronic nephritis; 19, diseases of metabolism; 20, skin diseases; 21, tuberculosis of the lungs.

overnutrition, undernutrition, visceroptosis, depression, and other conditions. Since this group is quite large and is composed of people of all ages without demonstrable organic disease, it may very well be

compared with patients with organic stomach disease or with other organic diseases.

The incidence of anacidity was 14.5 per cent, and when this group is compared with column A, there is a striking difference.

III. Anacidity in organic diseases other than disease of the stomach. In column C is shown the frequency of anacidity in people with organic disease other than that of the stomach. This group includes

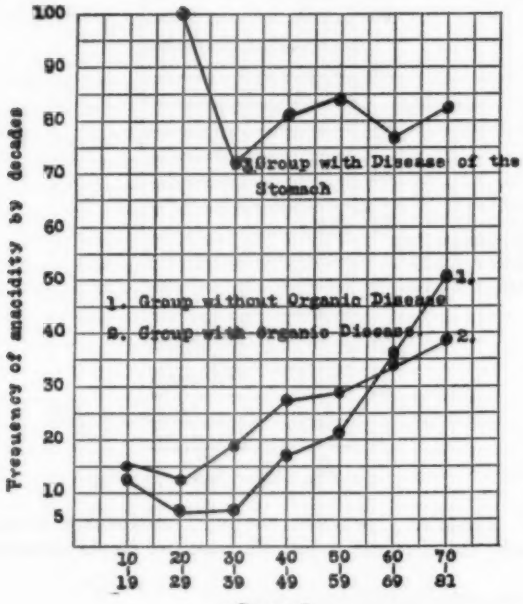


CHART 3

diseases of the intestinal tract, carcinoma other than carcinoma of the stomach, chronic arthritis, heart disease, renal and vascular disease, syphilis, tuberculosis, lung diseases, skin diseases, diseases of the nervous system, secondary anemia, hypo- and hyperthyroidism.

On comparing columns A and B, the difference in the percentage of instances of anacidity is striking, whereas, when column C is compared with column B, the difference is not very great.

Relation of anacidity to special diseases. In Chart 1, the general

relation of age to anacidity has been pointed out, and this must be taken into account in discussing the possible causal relation between special diseases and impaired gastric secretion. For this reason, we

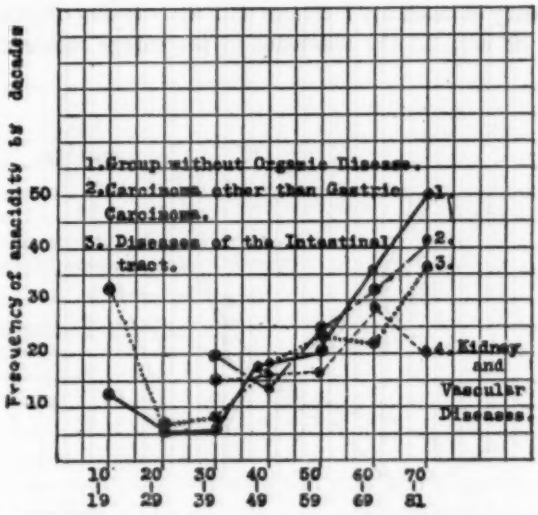


CHART 4. Carcinoma other than gastric carcinoma includes carcinoma of the pancreas, colon, prostate, liver, peritoneum, esophagus, ovary, rectum, bronchus, gall-bladder, antrum of Highmore, uterus, ileum, bile-ducts, tumors of bone, kidney, testicle, mesentery, retroperitoneum and cervical glands. Total cases 65; total percentage of anacidities, 22.4.

Diseases of the intestinal tract include chronic appendicitis, ulcerative colitis, duodenal ulcer, diarrhoea, amoebic dysentery, bacillary dysentery, liver abscess, syphilis of liver, rectal polyposis, chronic cholecystitis, with and without stones, cirrhosis of the liver, Meckel's diverticulum, stricture of rectum, carcinoma of pancreas, liver, colon, rectum, gall-bladder, peritoneum, ileum, bile-ducts, mesentery. Total cases 204, total percentage of anacidities, 15.8.

Diseases of the kidneys and blood vessels include hypertension, arteriosclerosis and chronic nephritis. Total cases 150, total percentage of anacidities, 17.1.

have summarized in Chart 3 the relation of age to anacidity, both in organic disease of the stomach, and in people without gastric lesions.

As might be expected, Group 3 shows a curve quite different from that of Groups 1 and 2. Group 1 will, in turn, serve as a control for comparison with individual diseases as shown in Charts 4, 5 and 6.

The charts indicate the frequency of anacidity according to decades, in different diseases. It becomes apparent at once that all of the curves follow more or less closely that of the group without organic disease. From these charts, the following conclusions seem justified. (1) Frequency of anacidity increases with age whether organic disease is present or not, (2) the difference in percentage incidence in the

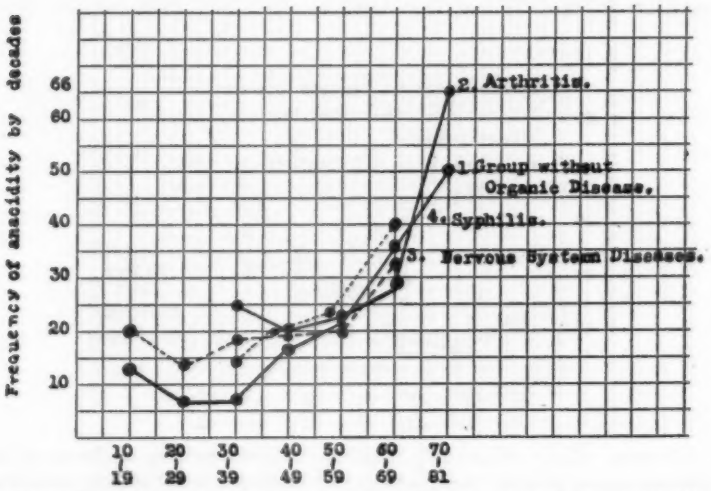


CHART 5. Arthritis includes cases of so-called chronic infections arthritis, arthritis deformans and hypertrophic arthritis. Total cases 94; percentage of anacidities, 18.4.

Syphilis includes syphilis of the liver, bones, and central nervous system. Total cases 30; percentage of anacidities, 17.8.

Diseases of the nervous system include epilepsy, multiple sclerosis, encephalitis lethargica, hemiplegia, multiple neuritis, progressive muscular atrophy, familial ataxia, neurofibromatosis, syringomyelia, paralysis agitans, general paresis and syphilis of the central nervous system. Total cases, 60, percentage of anacidities, 16.5.

various diseases is too small to be of any definite significance, (3) there is no definite evidence from this material that the diseases studied can in themselves influence the occurrence of anacidity.

To summarize, then, the essential findings in the study of this group are, first of all, that anacidity increases in frequency as age advances.

This is true whether organic disease is present or not. While the incidence of anacidity in patients with organic gastric disease is quite high in all decades, there is very little difference in people with organic extra-gastric disease and in those without any organic disease. Even

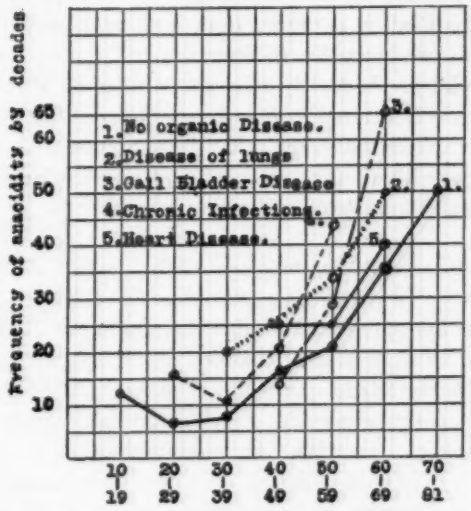


CHART 6. Disease of the lungs includes pulmonary tuberculosis, carcinoma of bronchus, bronchial asthma, chronic bronchitis, and abscess of lung. Total cases 26; total percentage of anacidities, 17.4

Disease of the heart includes valvular heart disease and the cardiac arrhythmias. Total cases 19; total percentage of anacidities, 15.8.

Disease of the gall-bladder, includes chronic cholecystitis with and without stones. Total cases 35; total percentage of anacidities; 20.7.

Chronic infections include tuberculosis of bones, lymph-nodes and lungs, perinephric abscess, pyelitis, abscess of abdominal wall, stomatitis, prostatitis, malaria, lung abscess, sub-acute bacterial endocarditis. Total cases 45; total percentage of anacidities, 17.8.

though the percentage of anacidities is somewhat higher in some of the groups with organic disease than in the group without organic disease, one is not justified in assuming, when the numbers in the respective groups compared are considered, that the difference is great enough to be of any significance. It may be stated, therefore, that

from this study there is no conclusive evidence that disease other than disease of the stomach can bring about gastric anacidity.

While it is true that observations are on record which show that during an acute illness, such as typhoid fever or influenza, gastric anacidity is present and later disappears, with the patient's recovery, one is not justified in assuming from such an observation that the gastric glands are incapable of secreting acid during the time when there is anacidity. It merely means that after an Ewald test meal, not enough acid is secreted to give the reaction of "free HCl." It will be pointed out later that when acid fails to appear with one stimulus, it may appear with another, showing that in many cases, the gastric glands are really capable of responding, provided the proper stimulus is given.

Relation of anacidity to symptoms. The present observations are based upon a study of 100 consecutive cases in which gastric anacidity was found in the course of a routine examination. These cases were studied in order to determine whether gastric anacidity in itself produced any characteristic symptoms or signs. In the 100 cases, the following diagnoses were made: Psychoneurosis, 38; hypertension, 21; hyperthyroidism, 4; arthritis, 14; undernutrition, 3; overnutrition, 2; depression, 2; gall-bladder disease, 2; carcinoma of prostate, carcinoma of stomach, ulcerative colitis, chronic proctitis, chronic myeloid leukemia, carcinoma of pancreas, pyelonephritis, hemorrhagic retinitis, carcinoma of colon, amoebic dysentery, arsenical poisoning, cirrhosis of the liver, cystitis, tabes dorsalis, menorrhagia, one of each.

In order to conserve space we have tabulated the results of this study in Table I. This table needs little comment, since it is quite obvious that there is no definite evidence from these observations that anacidity *per se* causes any specific symptoms or signs. Moreover, in each case in which diarrhoea or secondary anemia was present, an adequate cause other than gastric anacidity was found to account for it. The radiographic studies revealed many variations, as regards shape, position, and activity of the stomach. Here again, it is apparent that anacidity was not associated with any one type of stomach.

TABLE I

Analysis of the clinical findings in 100 consecutive cases of gastric anacidity

I. *Digestive disturbances:*	
1. None	54
2. Constipation	21
3. Diarrhoea	5
(a) Hyperthyroidism	1
(b) Amoebic dysentery	1
(c) Following rectal operations	2
(d) Ulcerative proctitis	1
4. Belching gas	6
5. Nausea and vomiting (All associated with hypertension)	7
6. Epigastric discomfort and fullness	7
II. *Condition of teeth:*	
Normal	65
Slight pyorrhoea	16
Absent	6
No note	13
III. *Condition of tongue:*	
Normal in all.	
IV. *Wassermann reaction:*	
Negative	98
Positive	2
V. *Blood examinations:*	
Normal R.B.C., W.B.C., and Hb	90
Secondary anemia	10
Conditions associated with secondary anemia:	
1. Arthritis	5
2. Carcinoma of stomach	1
3. Chronic nephritis	1
4. Leukemia	1
5. Pyelonephritis	1
6. Carcinoma of large bowel	1
VI. *X-Ray findings in 85 cases:*	
1. Nothing abnormal made out	57
2. Prolapse of stomach	12
3. Rapid emptying	3
4. Slow emptying	6
5. 15-hour retention	1
6. Filling defects	2
(1) Carcinoma of stomach	1
(2) Carcinoma of large bowel	1
7. Atonic stomach	4

PART II. EXPERIMENTAL OBSERVATIONS ON GASTRIC ANACIDITY

In the following part of this paper, we wish to describe certain observations made in cases of "anacidity" by means of the method previously described (3). Simultaneous studies of volume of secretion, of pH of secretion and of motility were carried out in the hope of discovering new facts about the pathology of the condition, and, perhaps new diagnostic criteria. Twenty-four cases of gastric anacidity were investigated. The original diagnosis was made in each on the basis of absence of free HCl in the gastric contents, as tested by di-methyl one hour after the standard Ewald test-meal. An attempt was also made to make a clinical decision as to the presence or absence of gross structural disease of the stomach independently of the results of gastric analysis.

The pH of the gastric secretion in anacidity

In making a diagnosis of gastric anacidity, it has been customary to use the reaction to di-methyl as a criterion. This indicator changes from orange to red at approximately pH 3.0, and serves admirably as a reagent for titrating acidity below this point; however, it obviously gives no information as to reactions within the zone extending from pH 3.0 to neutrality at pH 7.0 or beyond on the alkaline side. *A priori* there is no reason to believe that a stomach which does not secrete enough acid to give the mixed gastric contents a pH of 3.0 or lower is necessarily incapable of secreting hydrochloric acid; on the contrary, it is certain that an appreciable amount of HCl will be neutralized by the buffers of the test-meal and of the gastric mucus and that a pH of 7.0 or above might be found even when acid has been secreted. The determination of the so-called acid deficit attempts, inadequately, to answer this question.

It seemed quite probable that there might be a difference in the pathological significance of total failure or inability to secrete acid as against mere failure to secrete enough to give the red or "free HCl" reaction with di-methyl. The first problem which was studied, therefore, was that of the pH reached by the gastric juice in cases of anacidity as determined by di-methyl.

The tests were carried out with the alcohol meal exactly as described

in detail in the previous paper (3). Inasmuch as the meal itself has a reaction of approximately pH 6.0, one can not feel certain that acid has been secreted unless the pH of the stomach juice falls below this point, although, even at a pH above 6.0, the possibility is not excluded. Conversely, a pH of 7.0 or over may indicate total absence of acid or merely an excess of buffer substances (mucus). It should be emphasized that the test-stimulus itself contains no protein or other buffer substances.

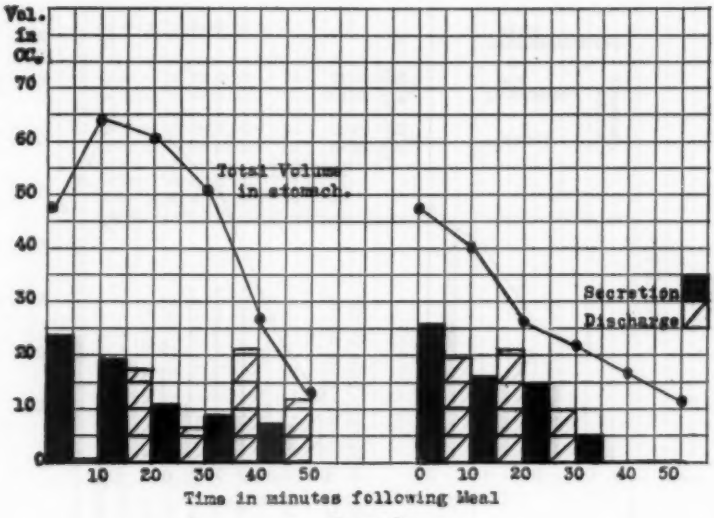


CHART 7

In Chart 7 and Table II are shown the complete protocols of an examination in order to illustrate the method as carried out in every case. This person (Case 54) had an "anacidity" according to the Ewald meal. The fasting secretion had a pH of 7.2 to 7.4, but after introduction of the test-meal, the reaction changed steadily and reached pH 6.4 after 40 minutes. It seems impossible to explain this finding except on the assumption that a small amount of acid was secreted. That this supposition was correct, was proved by a second examination in which the pH fell to 5.5. The patient, incidentally,

TABLE II

SPECIMEN NUMBER	OBTAINED	AMOUNT AND APPEARANCE	pH	TITRATABLE ACIDITY		TOTAL STOMACH CONTENTS	SPECIMEN RETAINED	AMOUNT RETURNED TO STOMACH	CONCENTRATION OF PHTHALEIN	AMOUNT OF JUICE SECRETED IN TEN-MINUTE PERIOD	DISCHARGED IN TEN-MINUTE PERIOD
				Dimethyl	Phenolphthalein						
				Examination I							
				cc. N/10 NaOH	cc. N/10 NaOH	cc.	cc.	cc.	per cent		cc.
1	Fasting	4 cc.—practically pure mucus	—	0.0	2.0						
2	Fasting—5 minutes after No. 1	3 cc.—practically pure mucus	7.2	0.0	2.0						
3	Fasting—10 minutes after No. 1	2.5 cc.—practically pure mucus	7.4	0.0	2.0						
4	5 minutes after meal	Clear fluid with much mucus	6.9	0.0	2.0	46	6	40	83		
5	15 minutes after meal	Clear fluid with much mucus	6.6	0.0	4.0	64	11	53	50	24.5	1.0
6	25 minutes after meal	Clear fluid with much mucus	6.5	0.0	4.0	56	10	46	35	20.0	17.0
7	35 minutes after meal	Clear fluid with much mucus	6.4	0.0	4.0	50	11	39	28	11.0	7.0
8	45 minutes after meal	Clear fluid with much mucus	6.6	0.0	4.0	26	7	19	21	9.5	22.0
9	55 minutes after meal	Clear fluid with much mucus	6.6	0.0	4.0	14	8	6	14	7.0	12.0
10	65 minutes after meal	Clear fluid with much mucus	6.7	0.0	4.0	22	—	—	Trace	—	

Examination II

1	Fasting after No. 1	25 cc. turbid white fluid with particles of mucus	7.4	0.0	–						
2	Fasting 5 minutes	6 cc.—turbid white fluid with particles of mucus	7.2	0.0	–						
3	5 minutes after meal	Clear fluid with bits of mucus	6.8	0.0	–	47	13	34	64		
4	15 minutes after meal	Clear fluid with bits of mucus	6.2	0.0	–	40	9	31	33	25.5	19.5
5	25 minutes after meal	Clear fluid with bits of mucus	5.5	0.0	–	26	9.5	17.5	21	16.7	21.0
6	35 minutes after meal	Clear fluid with bits of mucus	6.5	0.0	–	22	11	11	10	15.0	10.0
7	45 minutes after meal	Clear fluid with bits of mucus	6.8	0.0	–	16	8	8	7	5.0	0.0
8	55 minutes after meal	Clear fluid with bits of mucus	7.0	0.0	–	12	–	–	Trace		

S (No. *69*).
(No. 53).

had never had any symptoms of digestive disease and was in the hospital for the study of a bradycardia.

In Chart 8 (column A) are shown graphically the highest acidities reached after the alcohol test-meal in 24 instances of "anacidity."[3] None of the subjects showed free acid with di-methyl, but it is quite obvious that many of them secreted some acid. To emphasize this point, there are included in the chart the gastric reactions of eight people who, when tested by the Ewald meal secreted small amounts of free HCl. The pH in these instances lay between 2.0 and 3.0. It appears, therefore, that if acid secretion is expressed in terms of pH of gastric contents, every degree is found from the low pH of frank acid secretion up to neutrality and even alkalinity, and that titration with

TABLE III

Reaction of gastric juice in cases of "anacidity"

	ORGANIC DISEASE OF STOMACH	NO ORGANIC DISEASE OF STOMACH
Total	12	12
Acid demonstrable without histamine	1	10
Percentage	8.3%	83%
Total	4	7
Acid demonstrable with histamine	0	6
Percentage	0%	86%

di-methyl, which merely divides cases into those with pH higher or lower than 3.0, has no final bearing on the ability or inability of the stomach to secrete acid.

An attempt was next made to find out if the pH of stomach contents in "anacidity" cases bore any relationship to clinical evidence of gross organic disease. In column B, Chart 8, are shown the lowest pH reached in twelve tests of people under no serious suspicion of such organic disease, whereas in column C are recorded the results in twelve cases of verified carcinoma of the stomach and pernicious anemia. It

[3] It should be remembered that the pH scale is logarithmic and that pH 2.0 means ten times the acidity present at pH 3.0, one hundred times that at pH 4.0, etc.

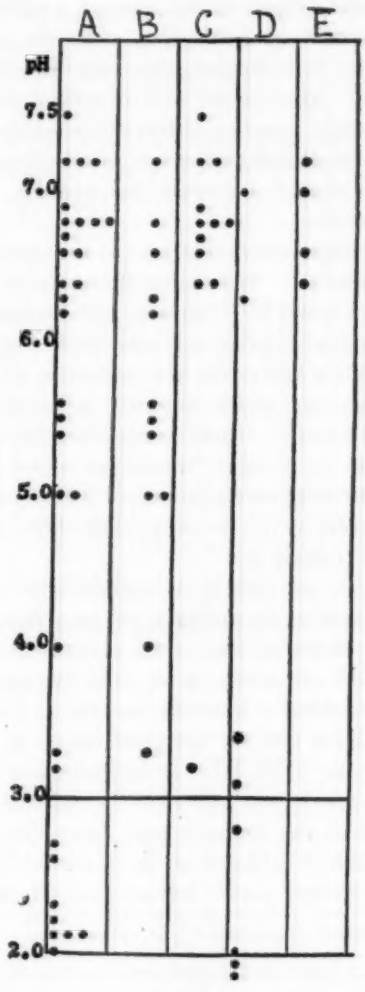


CHART 8

may be noted that in seven of twelve, or over 50 per cent, of the cases classified as "functional," the pH fell below 6.0, whereas in twelve

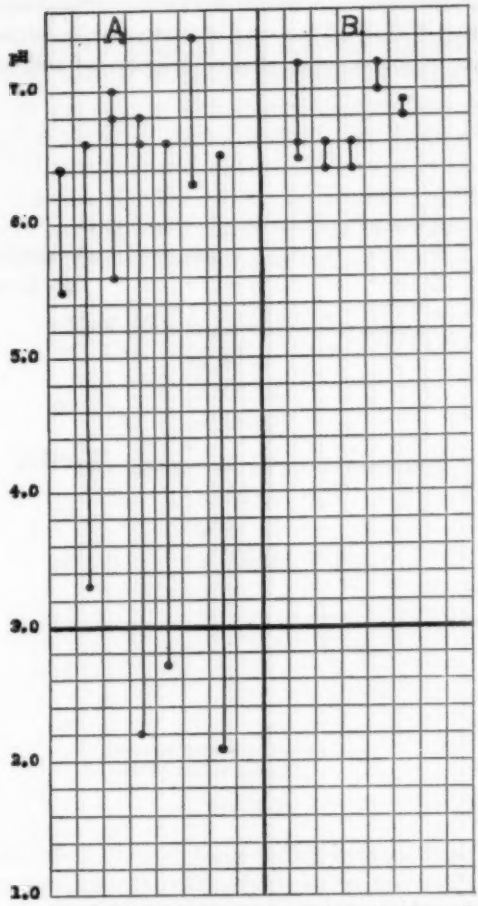
instances of "organic" disease of the stomach a pH of under six was attained only once (8.5 per cent)—in a man with carcinoma of the stomach (No. 260). It is evident, then, not only that people who have an "anacidity" when tested with di-methyl may secrete acid, but also that such slight secretion of acid occurs much more frequently in those who show no clinical evidence of gastric disease than in those who have a serious organic disorder of the stomach. The diagnostic implications are obvious.

In a further attempt to differentiate the two groups, the reaction to histamine was studied. The clinical literature on this subject has been adequately reviewed by Gompertz and Vorhaus (12). Suffice it to say that histamine injected subcutaneously is a powerful stimulant to gastric secretion and serves to demonstrate any latent capacity to produce such secretion which may exist in people who do not respond to test-meal stimuli. It may be seen from the results in column D, Chart 8, that in six of eight "functional" cases free acid was secreted after the subcutaneous injection of 0.5 mg. of histamine (ergamine), whereas there was no response in any of four definite instances of organic disease (column E).

In summary, then, we wish to re-emphasize the point that "anacidity" to di-methyl after the ordinary test meal does not mean that a complete inability to secrete acid exists, and that pH determinations after suitable stimuli are necessary to settle this question. Furthermore, there is a correlation between the clinical evidence of serious organic gastric disease and the complete failure to produce acid, as shown in Chart 8 and Table III. In assigning any diagnostic value however, to this correlation, one must be mindful that exceptions exist. Carcinoma of the stomach may occur, for example, in the presence of secretion of acid and we have seen at autopsy a case of ulcerative colitis without gastric lesions in which the pH never fell below 6.6.

Reaction of stomach juice on repeated examination of "anacidity" cases

In a previous paper (13) it was pointed out that repeated examinations, under standard conditions, of people without gastric disease revealed fairly constant values for the acid secretion of the stomach. It seemed of interest to find out if the reaction of the gastric juice was



pH of Gastric Juice on repeated examinations of Anacidity Cases. A. Functional B. Organic.

CHART 9

constant in individuals with "anacidity." Repeated tests were made in twelve patients who showed no free HCl with the Ewald meal. The tests were carried out under practically identical conditions with

intervals of a few days to a month between examinations. It may be seen in Chart 9 that all but one of seven people without clinical signs of disease of the stomach showed evidence of acid secretion on

CHART 10

the second or third examination; whereas, the group with organic disease failed repeatedly to produce acid. In three of the functional cases, free acid (di-methyl) appeared; in the others, it was necessary to determine the pH to demonstrate the acid secretion.

The volume of gastric secretion in cases of anacidity

Although clinicians speak of wet and dry achylias, no accurate observations of volume of gastric secretion in "anacidity" are on record. In 24 cases of the present series, satisfactory determination of the amount of secretion during successive ten-minute periods after the alcohol test stimulus were made. The procedure was that which has already been described in detail. In column A of Chart 10, each dot represents the average number of cubic centimeters of gastric juice secreted in ten minutes in a series of controls. As we pointed

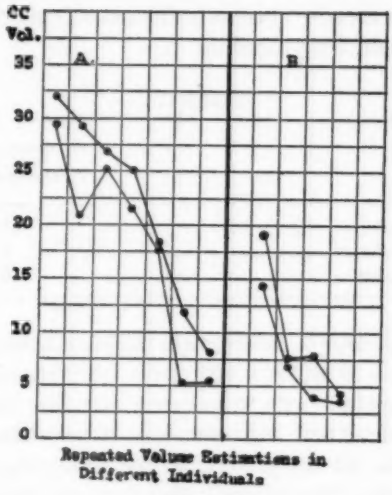


CHART 11

out previously, 89 per cent of these people secreted from 10 to 40 cc. of juice in ten minutes. In column B are shown the secretory volumes of 14 cases of "anacidity" in which no evidence of "organic" lesion of the stomach was present. The findings are to all intents and purposes identical with the control observations, 93 per cent of the volumes being between 10 and 40 cc. The results with the 10 cases of "anacidity" in people with pernicious anemia and carcinoma of the stomach (column C) are quite different. The tendency to low volume secretion is obvious and only 40 per cent of the observations fall

between 10 and 40 cc. It appears, therefore, that a ten-minute secretion of less than 10 cc. is evidence in favor of organic disease; whereas a secretion of over 15 cc. is presumptive of absence of gross gastric lesions.

No attempt was made to study the chemical characteristics of the secretion in "anacidity" cases, but, as a rule, the presence of mucus was obvious.

In curves A and B of Chart 11 are shown the results of repeated volume estimations in cases of "anacidity." The two dots in each vertical column represent two tests on the same person at intervals of a few days to a month. Just as in the controls previously reported, the volumes remain fairly constant.

TABLE IV

	VOLUME OVER 10 CC., ACID DEMONSTRABLE	VOLUME UNDER 10 CC., ACID NOT DEMONSTRABLE
Total cases	9	6
Clinical diagnosis functional	9	0
Clinical diagnosis organic	0	6

In a further attempt to differentiate the anacidities, the cases were divided into those in which a fall of pH after stimulation could be demonstrated together with ten-minute secretion volumes of over 10 cc., and into those with volumes under 10 cc. without a fall in pH. It was found that all the subjects in the first group were clinically regarded as having "functional" disturbances; whereas all in the second group had definite structural lesions of the stomach. These results are summarized in Table IV.

These combinations seem, then, to have distinct diagnostic significance.

Gastric motility in cases of anacidity

In a previous paper (13) studies of gastric motility following a standard alcohol meal were reported. It was pointed out that, among normal controls, there were great variations, both in the individual and in the group as a whole. These variations could not be

correlated with volume or with acidity of secretion. The emptying times of this control group are shown in column A of Chart 12. In column B are charted the emptying times of the present series of anacidity cases. It is apparent that, on the whole, the stomach empties more quickly in the anacidity group, although there are many exceptions. The difference in the groups is much less striking

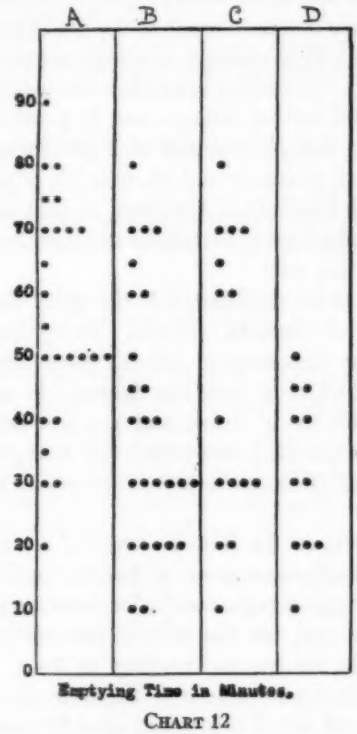


CHART 12

if the anacidities in patients without organic disease are considered apart (column C). In the anacidities with organic disease, on the other hand (column D), it is obvious that emptying tends to be rapid. None of these patients had pyloric obstruction. Most of the patients with rapid emptying secreted very small amounts of juice, and calcu-

lations of the volume of gastric contents passing the pylorus in a ten-minute period show it to be, on the whole, less than in more slowly emptying stomachs with greater volumes of secretion.

GENERAL DISCUSSION

In the light of the data presented above we may now return to the original question of the significance of gastric anacidity. It appears, first of all, that when determinations of the pH of gastric contents are made, many persons with apparent anacidity are actually found to be able to secrete acid. When the histamine test is applied, the number of anacidities is still further reduced and in point of fact the group becomes practically limited to people with definite anatomical disease of the stomach, such as cancer and the gastritis of pernicious anemia. The point of prime importance, therefore, in clinical work is to make studies which are adequate to determine whether the stomach is really incapable of secreting acid.

The next point to be emphasized is the great variation in gastric acidity in groups of "healthy" people. Every degree may be encountered from the conventional normal values (free HCl 40 to 60 or more; pH 1.2 to 1.4) to very low figures. In a word the actual normal is very difficult to define and the question may be raised whether absence of free HCl (di-methyl) can in any sense be regarded as abnormal unless there are other evidences of gastric disease or deficiency.

Turning, however, to the facts as revealed by a study of Ewald test-meals in a miscellaneous group of hospital patients we have been unable to discover any definite correlation between anacidity and any other factor except age, nor has it been possible to prove that any digestive symptoms are due to anacidity in itself.

From the standpoint of practical diagnosis the determination of secretory volume and of pH before and after histamine is essential, if information of any value is to be obtained. The combination of low secretory volume with complete absence of acid is practically diagnostic of serious organic disease of the stomach, whereas large secretory volumes tend to rule out such disease with the exception of gastric ulcer.

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THE PLACE OF R.-J.-H. DUTROCHET IN THE DEVELOPMENT OF THE CELL THEORY[1]

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In the year 1839, there appeared from the pen of a young man, 28 years of age, a small book containing a generalization which, in its profound and far-reaching influence upon medical and biological thought, ranks with the very greatest of the discoveries made during that Golden Age of medical history, the nineteenth century. The author of that monograph was Theodor Schwann, a favorite assistant in the Berlin laboratory of Johannes Müller; the title of the work was "Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants"; and the epoch-making generalization which it contained was the now familiar fact that all of the living tissues of animals and of plants are composed of a multitude of individual living organisms, the cells. This doctrine of the cell as the ultimate unit of life electrified contemporary biology and medicine. It swept rapidly around the world, meeting serious opposition in no quarter. Schwann's fame was immediate, and his "cell theory" was hailed enthusiastically as an immortal contribution to science. In all medical history there is hardly a parallel instance in which a pronouncement of such import encountered so little opposition before being accepted everywhere as an established fact.

We today, who have been trained from our earliest contacts with biology to think naturally in terms of cells, can hardly reconstruct in our imagination the invigorating effect of the vistas which were suddenly opened up to those living when Schwann's book appeared. If Bichat's decentralization of the living principle from the body as a whole to the various individual tissues was a stirring event, the further decentralization of the life of each tissue into myriads of separate, individual lives, was nothing short of breath-taking. It was realized at once that, since the activity of any tissue is merely the sum of the

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activities of its numberless component units, the cells, in order clearly to understand the physiology of an organ the structure, arrangement, properties and potentialities of its fundamental units had to be known. Tissues of every description, therefore, began to be subjected systematically to the most painstaking scrutiny with the microscope, and the science of histology was born. Attempts were made to explain function on the basis of the discovered microscopic structure, and the very foundations of physiology were reconstructed. It required but little imagination to apply the microscope to the comparison of diseased tissues with normal ones, and Müller, Henle and numerous others did not delay in doing so; but it was obviously impossible for such studies to be correlated or systematized before a sufficient series of facts regarding the structure of normal tissues had been accumulated. Nearly twenty years passed following the publication of Schwann's monograph before histology had advanced to a point which permitted a satisfactory systematic survey of pathological processes from the standpoint of the "cell theory," but during those years the importance of the cell in the interpretation of pathological processes was never lost sight of. The wood-cuts of normal and pathological cells which are to be found in practically every textbook of pathology printed during that period, and, especially, the titles and contents of such works as the *Icones histologiae pathologicae*, published by Vogel in 1842, the *Pathologische Gewebelehre*, written in 1845 by Günsburg, the *Grundzüge der pathologischen Histologie* by Wedl in 1854, and Förster's *Atlas der mikroskopischen pathologischen Anatomie* of the same year, although all long since forgotten, serve today to instruct us in the clearest manner regarding the gradual development of the concept of "cellular pathology." Virchow, who, in 1858, finally built the permanent foundation of that science in so masterly a fashion, relates that he began his medical studies just after the appearance of Schwann's book, at a time when "the scientific atmosphere was still entirely filled with the new ideas. Johannes Müller, our honored Master . . . . was the first who introduced them, in the broadest way, into pathology, for he applied the same methods to the study of tumors. What wonder, then, that we, his disciples, learned early to think in terms of cells!" (5).

Besides the vast new fields in anatomy, physiology and pathology

which were opened up by the cell theory,[2] the science of embryology found in it its true orientation. Furthermore, comparative embryology and histology soon revealed important bonds between widely different animal species, and indeed even between animals and plants. Through these channels the cell doctrine became a factor much more important than is commonly appreciated in paving the way for the acceptance of that important theory which had lain dormant for so long in the works of Lamarck, Treviranus and others—the doctrine of organic evolution; and, ever since, comparative cellular studies have continued to add fact on fact to the support of that remarkable concept.

The possibilities opened by the cell theory are, indeed, well nigh inexhaustible. Numerous entirely new fields of science depending upon it lie even yet untouched, waiting either for workers to apply themselves, or for the progress of necessary, collateral sciences. The development, for instance, of such an obviously important branch of medicine as comparative pathology has not yet been even begun. Indeed, after the lapse of nearly a century of intense effort, we remain almost completely ignorant of the properties and potentialities of most of those little organisms which unite their efforts so perfectly in the production of that which we call the "life" of the bodies of animals and plants. We have hardly passed the threshold of the cell membrane. Our information in physiology has to do chiefly with extracellular materials, with products and waste products of cells and with cellular energy; and there is even a tendency at present either to ignore the marvellous activity of the cell itself, or else to offer a few simple physical and chemical laws as an explanation of many of the complex powers of living protoplasm. The series of ripples started by the cell theory have not, however, ceased to widen out over the surface of biological thought, and one meets even now with occasional papers in which the attempt is made seriously to probe, by direct observation and experiment, into the inner workings of the cell itself. These are the harbingers of a new science which cannot fail to bring us closer than we have ever been to the understanding of life.

[2] Although the doctrine of the cell as the unit of life has long since ceased to be a theory, the term 'cell theory,' nevertheless, survives as the standard expression for that doctrine.

II

It is always a matter of interest to trace out the succession of events leading up to the crystallization of any concept which has succeeded in changing permanently the form of human thought. In the case of the cell theory, time has so celebrated the name of Theodor Schwann that it is customary to believe that the idea sprang, Minerva-like, full-formed and original, from out the substance of his single brain. Indeed, so closely is Schwann's name linked with the term "cell," that it is hardly surprising that the writer of an obituary editorial in the *Berliner Klinische Wochenschrift* of 1882 felt it necessary to attempt to correct the prevalent belief that it was Schwann who first discovered and described the cell. Had Schwann's book ever been widely read, no such correction would have been necessary; for it begins with a brief historical summary which, although singularly incomplete and inadequate, nevertheless contains references to numerous preceding investigators to whom the cell was a perfectly familiar object. But, curiously enough, in spite of the immense popularity of a part of its contents, the book itself was read by relatively few persons. There was not even a demand for it sufficient to encourage the printing of a second German edition. The kernel of truth contained in it seems to have been passed on from person to person, and quoted from book to book. The many errors which it contained were dropped as soon as they were recognized, and quickly forgotten. Few today, for example, have ever heard of Schwann's completely fantastic and erroneous "proof" of the manner of origin of new cells, and yet that extensive series of observations constitutes the very portion of the book upon which he laid the greatest stress, and that which he himself regarded as his most important contribution.

The story of the cell theory begins, properly, about the middle of the seventeenth century, when that bewilderingly versatile Englishman, Robert Hooke, turned his attention to the improvement of the crude microscopes which were regarded, at that period, merely as amusing optical toys. His omnivorous curiosity soon became ensnared by the fact that it was necessary only to look through his magnifiers at almost any object about him in order to see remarkable things which human eyes had never before discerned. Although

Hooke really made a sincere effort to elevate the use of the microscope to a level of dignity higher than that of a gentle pastime, his manner of presenting the results of his observations leads one to suspect that, among his many other talents, he must have had in his make-up something of that manifestation of the journalistic instinct which finds its outlet today in the editing of the photogravure section of our Sunday newspapers; for, in 1667, he published a most curious and surprising volume entitled "Micrographia," in which the many extraordinary, unrelated and quaintly described subjects of his microscopic studies follow, pell-mell, one on the heels of another, with about as much congruity as exists between "shoes and ships and sealing wax." In this work there appeared, for the first time, a brief description and a very hazy sketch of the cellular structure of an organic tissue. The subject of this particular study of Hooke's was a bit of cork shaving; and he described it as being made up of an agglomeration of "little Boxes or Cells distinct from one another," and, again, as "an infinite company of small Boxes or Bladders of Air." The little boxes in that dried-out plant tissue were, of course, entirely empty; and, although he mentions having seen in other plant tissues some which were "filled with juices," he really had no notion whatever of the cell as a living unit of complex structure and function. It is a proper estimate of Hooke's contribution to say that its importance lay not so much in the recognition of the cell as the ultimate living unit of tissues, as in the stimulating observation that an apparently continuous organic tissue may be found to have a very curious and complex minute structure if examined with the microscope.

Because of the large size of most plant cells, and of the fact that the microscopic examination of plant tissues offered distinctly fewer technical difficulties than that of animal tissues, it devolved naturally upon the botanists to carry our knowledge of cellular structure through its infancy. Thus, although Leeuwenhoek, Malpighi, Lieberkühn, Prochaska, Fontana, Hewson and others made interesting, but for the most part rather gross and indefinite observations upon some of the tissues and free cells of the animal body, the beautiful botanical studies of Malpighi and of Nehemiah Grew, toward the end of the seventeenth century, followed, after a sterile hiatus

of more than a hundred years, by the investigations of Mirbel, Sprengel, Link, Treviranus and Rudolphi, succeeded in establishing clearly the important fact that every living plant tissue is composed of a multitude of little cellular vesicles which contain the living matter of the part in question.

This, then, was the state of information regarding cells in the early years of the nineteenth century: all living plant tissues were known to be composed of vesicular cells; a few animal tissues were known to contain so-called "globular corpuscles;" of these "globular corpuscles" only the red blood cells were believed to have a "cellular," or vesicular, structure resembling that of plants. But what of the elementary structure of the animal body, as a whole? It remained, essentially, an unexplored field. Of course, there had not been lacking certain philosophers, such as Leibnitz, who, purely for the narrow uses of their own particular philosophic systems, had not hesitated to assume that every part of the animal body is made up of myriads of little individual units; but inventions such as the "monads" of Leibnitz were merely crass hypotheses, based upon no germ of scientific observation. Scarcely more can be said of Oken's easy assurances that the body is made up of countless little microscopic animals, each of which sacrifices its individuality for the welfare of the whole being.[8] In 1823, however, there appeared the first scientific attack on the question. J. B. Dumas, who was himself interested in microscopic studies, suggested to Milne-Edwards, then a medical student in Paris, that he build his doctorate thesis upon a

[8] Oken maintained that all animal and plant tissues are composed of "weichen Bläschen, dort schleimig, hier mehr gallert- oder eyweissartig," that these "Bläschen" are living "animals," and that "das Zellgewebe der Pflanzen ist daher nichts anders als ein Haufen von Urpflanzen. Dieselbe Bedeutung hat das Zellgewebe des Thiers." (7). Since Oken has occasionally been regarded as a forerunner of the cell theory, it may not be out of place to recall that he reached this conclusion by way of the nimble reasoning that, since millions of infusoria appear during the putrefaction of dead tissues, and since spontaneous generation is not to be invoked as the source of them, it must be true that the tissues are composed of these little animals, which, at the death of the body as a whole, become able to regain their individuality! "Wenn alles Fleisch zerfällt in Infusorien, so lasst sich der Satz umkehren, und es mussen alle höheren Thiere aus diesen als ihre Bestandtheile bestehen" (8).

survey of the principle tissues of the animal body, with the distinct purpose of investigating their elementary structure. To this Milne-Edwards applied himself; and he saw that every animal tissue upon which he turned his microscope was composed of "spherical corpuscles about $\frac{1}{100}$ of a millimetre in diameter, which, by their assemblage, make up all of the organic tissues no matter what their properties or what the functions which they are destined to perform" (9). Unfortunately, this maiden thesis, besides displaying an immaturity and superficiality inconsistent with the very excellent later work of this investigator, contains no suggestion whatever which permits one to believe that Milne-Edwards had even remotely penetrated the meaning of the structure of the tissues which he studied. Indeed, the twenty-seven illustrations which accompany his thesis are quite conclusive proof, for the writer at least, that he had never really seen an animal tissue-cell under the microscope. But even if it be granted that his "spherical corpuscles" were tissue cells, and not the optical deceptions which had so carefully to be guarded against in those days of crude microscopes and cruder technical methods, one lays aside the little paper with the feeling that its only virtue is contained in the fact that, for the first time, an effort had been made systematically to examine the various tissues of the animal body in an attempt to acquire information concerning their microscopic structure.

My purpose in writing this paper is to insert at this point in the history of the development of the cell theory the name and the work of a forgotten investigator who, by careful observation and experiment, and by penetrating reasoning, was led to formulate the cell theory in the clearest manner, at a time when Theodor Schwann was still merely an adolescent schoolboy. Most medical historians find him worth not more than a line or two in their critical catalogues of great men, and they offer no suggestion of his real contribution to the cell theory. Specialists in histology and in all branches of medicine have completely ignored his work, if, indeed, they were ever acquainted with it. Few of the present generation have even heard his name. So does oblivion not infrequently close over the memory of those who have been imprudent enough to speak a fundamental truth before the ears of their contemporaries have begun to listen expectantly for it.

III

René-Joachim-Henri Dutrochet was born on the fourteenth of November, 1776, in the Chateau de Néon, situated in the department of Indre. His father, René-Louis-Frédéric, Comte du Trochet and Marquis de Néon, was an infantry officer in the king's regiment. His mother, Madeleine-Charlotte-Marie de Gallois, belonged to a distinguished and wealthy family of Touraine.

Dutrochet (for so he chose to write his surname throughout his life) was born with an extreme deformity of the talipes equinovarus type, which medical authorities were unwilling to attempt to correct, considering it irremediable. In Vendôme, however, there lived a layman named Montaigne who, according to popular belief, possessed a sovereign method of reducing fractures. He was, apparently, one of that curious order of "bone-setters," who have practiced their secret art, often with remarkable success, for centuries. Dutrochet's mother, following a slender hope, took him to Vendôme and placed him under the care of this Montaigne, who broke and reset the infant's feet. The functional result was excellent and permanent.

Most of Dutrochet's infancy was spent in Chareau at the country house of his maternal grandmother, the haven in which he was destined to live and to work during the best years of his life. When nine years old he was sent to the Collège de Vendôme, where he finished his studies with honors at the age of fifteen.

During the latter years of Dutrochet's term at Vendôme, France was shaken by momentous events, beginning with the convocation of the States-General and culminating in the storming of the Bastile. Shortly after his graduation the Revolution reached the height of its frenzy and, during the Terror, the du Trochet and de Gallois families, royalists to the end, were almost completely impoverished. They were stripped of all their possessions except the maternal homestead at Chareau, and Dutrochet's father had to flee the country to save his life.

After the Revolution, Dutrochet was conscripted into the naval service of the Republic. In 1799, when the Directory was hopelessly tottering, and the rapidly growing royalist army, in which his brothers were zealous officers, was daily gaining recruits from the Republican

forces, Dutrochet, then twenty-three years old, was persuaded to desert the service of the Republic for the royalist cause. The smouldering civil war was shortly afterwards extinguished by Napoleon's memorable *coup*, temporary peace was established, and Dutrochet returned to Chareau, where, for two years, he lived idly, occupied only with the amusements of the chase. It was at this point that there occurred the first of the three fortuitous events which served to direct his life toward the study of biological problems. It consisted in his forming a chance acquaintanceship with a Parisian surgeon, Dr. Petibeau, who had temporarily taken a house near his mother's estate at Chareau. Petibeau, who appears to have been a sympathetic and discerning man, was strongly attracted to young Dutrochet whom he found impatient with his protracted idleness, and anxious to pursue some interesting occupation, but in such straitened circumstances that he was beginning to despair of ever being able to obtain special training. Petibeau accordingly offered to help him to acquire a medical education, placing at his immediate disposal an unoccupied room in the Paris Children's Hospital, in the rue de Sèvres, of which he was surgeon-in-chief. Dutrochet eagerly accepted the generous offer, and in 1802, at the age of twenty-five, he set out for Paris to begin his medical studies under the close supervision and friendly guidance of his patron. Four years later he obtained his doctor's degree. His thesis consisted of an original and ingenious attempt to explain the mechanism of the human voice. Several years later he extended his ideas on this subject by developing a new theory of harmony.

In 1808, intending to practise his profession as a means of livelihood, he chose the career of an army surgeon, and left Paris to join a regiment dispatched to the support of Joseph Bonaparte, the newly-made King of Spain. When the regiment reached Burgos, the second of the determining accidents in Dutrochet's life occurred in the form of an epidemic of typhoid fever which ravaged the troops. A Dominican convent was hastily converted into a military hospital in which Dutrochet served as physician-in-chief; but he soon fell prey to the disease himself. His health was so undermined by the malady that he was forced to return to France and to retire permanently from active work. He resigned from the service, and went back once again to live with his mother and his sisters at the old family home in Chareau.

He was now thirty-four years old. His doctorate thesis had given him a taste of the pleasures of the application of reasoning to scientific problems; fortunate chance, acting for the third time, now placed in his hands the works of Spallanzani, which impressed him powerfully with the value and possibilities of direct experiment. From that moment Dutrochet's path lay clear before him. During the succeeding twenty-five years of his life, in a simple, makeshift laboratory in his mother's house, he devoted himself unremittingly and alone, to the experimental study of a wide variety of important subjects in the realm of natural history. He communicated regularly the results of his investigations to the Paris Academy of Sciences, of which in 1820 he was made a corresponding member.

His first notable work was a comparative embryological study, in which he demonstrated connecting links between the development, structure and functions of the foetal membranes of birds, reptiles, and mammals, stressing the fact that the allantois, which, in birds, is applied to the shell for purposes of respiration, develops in mammals into the placenta with its analogous respiratory function. Then followed, among other papers, careful studies on the metamorphosis of the tadpole, the development of the alimentary canal of insects, the formation of the chalazae of the avian egg, the anatomy of the reproductive organs of the aphis, the structure and development of feathers, the mechanism of muscular contraction. His papers on osteogenesis, and on the growth and reproduction of plants, were both crowned by the Academy. His interest in plant physiology was intense, and he strove continually to demonstrate bonds between the living processes of animals and those of plants, stressing repeatedly the idea that comparative physiological studies should, whenever possible, be extended to include plants as well as lower animals. His own contributions to plant physiology were numerous and important, and are discussed in every comprehensive treatise on the subject. "With the exception of Theodor de Saussure, who was occupied exclusively with questions in physiological chemistry, Dutrochet was the only person in the 1820's and 30's who applied serious thought and experiment to the important problems of plant physiology," wrote Sachs, in 1875, in his well-known "Geschichte der Botanik." "In order to appreciate the status of Dutrochet as a plant

physiologist during the thirties," he continues, "it is necessary only to compare his works with the best textbooks of plant physiology of the same decade—with those, for instance, of De Candolle, Treviranus and Meyen. None of them approach Dutrochet's '*Mémoires*' in sagacity and depth."[4]

He was one of the pioneers in the study of tropisms, discovering apheliotropism independently, before he learned of the earlier experiments of Knight. He also investigated minutely the tropic effects of gravity, of different light rays, and of moisture. Among his many other important studies are experiments on the movements of plants, the mechanism of the ascent of sap, on plant "sleep," and on the function of the pneumatic cavities. He demonstrated that mushrooms are aerial fruits of a subterranean byssus; and carried out extensive researches in plant embryology. He had a strong appreciation of the value of the microscope, and it was his incessant use of it that led to his two most important discoveries. Before entering into a discussion of his relation to the cell theory, however, I shall record, briefly, the remaining important incidents in his life.

His health was never sound. For years he suffered from some undetermined cerebral affection which tormented him with continuous violent headaches, and even impaired his ability to write. To Dutrochet, who regarded the careful recording of notes as an absolutely essential part of scientific investigation, this latter infirmity was a matter of greater concern than were the distracting headaches. He therefore set about to arouse the interest of a young villager in his experiments, and after he had taught the youth to read and to write, he was able to enter again into his tireless experimenting, with the assistance of this rustic amanuensis. At Chareau he was never occupied with the active practice of his profession, but his medical knowledge was always at the disposal of the poor; and, during the great cholera epidemic of 1832, he closed his laboratory and hastened to a neighboring stricken town in order to assist in the battle against the plague.

In 1831, at the age of 55, his many important studies had made

[4] It is extraordinary that even Sachs, with all his admiration for Dutrochet's work, leaves Schwann's fame untroubled by any reference to Dutrochet's investigations on the importance of the cell.

him known as one of the foremost physiologists of his time, and he travelled to Paris to be received into the Academy as a titular member. He was also made a member of the Legion of Honor. He was unable, however, to remain in Paris among his colleagues, for he was too poor to bear the expense of even a simple life in the capital. It was therefore necessary for him to return to his isolated laboratory, where he immediately occupied himself again with new experiments. Two years later his mother died, and with his inheritance he might have gratified his gnawing desire to return to Paris; but instead he divided his portion so generously among his brothers and sisters that too little was left for himself to enable him to leave Chareau.

Some years previously, Dutrochet had attacked openly a certain scientific opinion held by Étienne Geoffroy Saint-Hilaire. That eminent naturalist promptly arranged an interview with him in order to talk over their differences. The result of this conversation was that Geoffroy St.-Hilaire conceived so great a respect and affection for Dutrochet that it was he, himself, who proposed the latter's name to fill the first vacancy in the Academy. The two scientists remained lifelong friends, and it was through the delicate manoeuvring of Geoffroy that Dutrochet, in 1833, then 57 yearsold, entered into a convenient but happy marriage with a charming and wealthy Parisienne. With her he left Chareau, for the last time, to take up his abode in Paris, where their house in the rue de Braque became the center of many brilliant assemblages. Dutrochet exerted himself particularly in the encouragement of a group of young investigators who looked to him for his thoughtful criticism and advice.[5]

His marriage was a very sympathetic one, and he may indeed be said to have "lived happily ever after." In contrast to his solitary laboratory in Chareau, he was now surrounded by colleagues, friends and disciples. Penniless and in want from his youth, he now possessed all material comforts. The long suppressed desire to live once again in the Paris that he loved was gratified. He did not close the period of his productive work with the door of the little labora-

[5] It is especially to a biographical sketch written in 1866 by one of these disciples, J. J. M. Coste, that I am indebted for information regarding Dutrochet's private life. Coste based his sketch upon an unpublished manuscript left by Dutrochet entitled "Notice sur ma vie et mes oeuvres" (12).

tory at Chareau; he was occupied continually up to his last illness with his biological investigations, and his papers during this period are numerous and significant. He died, without issue, on February 4, 1847, at the age of 71.

The scientific writings of Dutrochet indicate clearly the manner of man that he was. That his genius was of a very high order cannot be questioned by anyone who reads his works. He was not one of those whose interest in science is so perishable as to require the shelter of a luxuriously equipped laboratory. He belonged, rather, to that hardy race of investigators whose absorbing curiosity has been a sufficient substitute for lavish material facilities. He was passionately devoted to scientific inquiry for its own sake. The opening paragraph of his collected works reveals a glimpse of his credo as a scientist, which will be appreciated and understood as long as there are men who find it necessary to spend their lives in the attempt to understand the natural phenomena about them. It is not utilitarianism, nor ambition, nor hope of fame, nor even the desire to assist mankind, which he stresses as the immediate stimulus to investigation. Whatever may be the rôle which these motives play in scientific inquiry, Dutrochet points first to a simpler and more direct one—the *pleasure* of investigation, which may be likened to the pleasure of the creative artist. This introduction, written in a calm, dignified and sympathetic style, sketches in sweeping strokes the problem of organic nature in a manner well worth reading today if only for the fact that the century which has passed since it was written has brought us gradually, through the work of many other investigators, to the acceptance of most of the ideas which it contains. Dutrochet was rigorously self-critical. He was not one of those whose motto seems to be "My theory—may it be ever right; but right or wrong, my theory!"—those familiar and pathetic figures who, holding their personal fame above the truth, find it almost impossible to admit the presence of error in anything that they ever put into print. He modified his expressed opinions as rapidly as he discovered anything erroneous in them, and openly printed upon the title page of his collected works a notice to the effect that every difference which existed between that edition and his original papers should be construed as a correction of one of his errors of observation or deduction.

While no one has ever been more painstaking or patient in making individual observations, or more conscious of the worth of the most minute individual scientific fact, yet Dutrochet strove continually to associate his isolated discoveries in the construction of broad generalizations. It was this tendency which led him to formulate and to realize the physiological importance of the cell theory for the first time.

IV

In order to make it clear that Dutrochet was the first really to fathom the meaning as well as the fact of the cellular structure of all animal tissues, it will be necessary to quote rather fully from his works, and to compare occasionally his conception of the problem with that of Schwann. These quotations will show, I believe, that 15 years before the publication of Schwann's monograph, Dutrochet

1. Established the anatomical individuality of tissue cells.
2. Described the universal cellular structure of living animal and plant tissues.
3. Demonstrated that certain lifeless structures, such as feathers, are originally composed of living cells.
4. Stressed the importance of the cell as the *physiological* unit of animal and plant tissues.
5. Maintained that growth consists in the formation and expansion of new cells.
6. First observed the migration of the leucocyte and originated the term "wandering cell."
7. Independently discovered osmosis, and was the first to study the conditions under which it operates, and to point out its importance in cellular metabolism.
8. Originated the term, and defined the outlines of the science of "general physiology."
9. Formulated a mechanistic concept of life identical with that of Schwann.

In 1822 and 1823 Dutrochet was occupied with microscopic studies the results of which he communicated to the Paris Academy, and assembled in 1824 in a monograph entitled "Anatomical and Physi-

ological Researches on the Minute Structure and the Motility of Animals and Plants." At this period, as has been said, it was well known to botanists that all living plant tissues are composed of cells. There were, however, differences in opinion regarding the nature of cellular tissue. Grew (10) in 1682, reached the conclusion that the cellular tissues of plants are fundamentally continuous, and compared the structure of the "infinite Mass of little *Cells* or *Bladders*" with that of the "Froth of *Beer* or *Eggs*." According to this idea, adjacent cells would have a single, common wall between them. On the other hand, Treviranus, among others, had observed occasionally the presence of intercellular spaces; and he advanced the theory that plant tissues are composed of separate juxtaposed cells. This idea was supported by Link, who had observed that, in a few instances, tissue cells could be separated from their fellows by boiling in water. These isolated observations, however, had little influence upon contemporary thought. Mirbel, the distinguished botanist who contributed so much toward establishing the general principle of the cellular structure of plant tissues, was led by his own extensive studies to support the correctness of the froth simile, and the influence of his authority at the beginning of the nineteenth century was largely responsible for the general acceptance of this view. Dutrochet, however, made the discovery that by boiling any plant tissue in nitric acid the cells could be separated from each other, and be seen to float about as distinct entities, each with its own walls and contents, and he insisted on the recognition of cells as separate, individual units. After a short controversy, Mirbel himself was convinced of the correctness of this observation, and it was then rapidly accepted by botanists in general. To Dutrochet, therefore, belongs the distinction of having established the important fact that every tissue cell is a separate individual anatomic unit.[6]

[6] The idea of the existence of a definite cell wall, which was regarded by both Dutrochet and Schwann as necessary for the proof of the individuality of cells, and to which they attached so great an importance in the life of the cell, lost much of its popular favor in 1863, when Schultze made it clear that animal tissue cells may be merely masses of protoplasm, instead of little boxes filled with fluid contents. It then became fashionable to ignore the importance of the cell wall, and to contrast the virtues of the "modern" view with the errors of the discarded,

Dutrochet now possessed the information and the qualifications required for the conception of the cell theory. He was an ardent microscopist; he had long been a student of animal physiology; his guiding principles had steadily been the belief in the value of comparative studies and the idea that the physiological processes of animals and of plants must exhibit fundamental resemblances. He had now become, through his botanical studies, thoroughly familiar with, and had made an important contribution to, the cellular structure of plant tissues. What more natural than that he should next turn his microscope upon animal tissues, with the purpose of seeking in them the cells which he had just succeeded in isolating from the tissues of plants? He appears to have been hardly surprised to find that animal tissues are, in fact, composed of cells. After relating his microscopic observations, he gives expression to the morphological substance of the cell doctrine in the following manner:

"I must repeat here that which I have stated above regarding the organic texture of plants: we have seen that plants are composed entirely of cells, or of organs which are obviously derived from cells; we have seen that these cells are merely contiguous, and adherent to each other by cohesion, but that they do not form a tissue actually continuous. The organic being has appeared to us, therefore, to be composed of an infinite number of microscopic parts, which are related only by proximity. Now the observations on animals which we have just described obviously confirm this view" (1).

"In the organs of vertebrates, the globular corpuscles are so small that it is impossible to know whether they are solid or vesicular bodies; but in molluscs that is very easy to determine. When one examines microscopically the tissue of the liver, the testis, or the salivary glands of Helix or of Limax, one sees that these secretory organs are composed, like those of vertebrates, of little globular bodies assembled in a confused manner; but here these little globular bodies are not so excessively small. They are indeed quite large (if one may use such an expression in speaking of microscopic objects), and one can see in the clearest manner that they are vesicular bodies, or true cells, the walls of which contain other very minute corpuscles.[7] One might perhaps doubt that these globular

original one. It is interesting that the advance of the science of physical chemistry has, through information regarding the phenomena of interphase boundaries, led us back again to a realization of the great importance of the limiting surface of the cell, even though it be not actually a tough box-like membrane.

[7] May not these smaller "corpuscles" seen by Dutrochet have been nuclei? The nucleus of fixed tissue cells was not definitely discovered until eight years

cells are the analogues of the globular corpuscles which are found in the secretory organs of vertebrates, but the most superficial examination will dissipate all such doubts, for one will see that the globular cells of the secretory organs of molluscs and the globular bodies of the secretory organs of vertebrates constitute, respectively, the entire parenchyma of these organs; masses of them surround both the blood vessels and the excretory ducts. One can therefore draw the general conclusion that the globular corpuscles which make up all the organic tissues of animals are really globular cells of an extreme smallness, which are united only by cohesion. Thus all the tissues, all the organs of animals are really only a cellular tissue diversely modified. This uniformity of ultimate structure proves that organs really differ one from the other only in the nature of the substances which are contained in the vesicular cells of which they are composed" (1).

"All of the organic tissues of plants are made of cells and observation has now demonstrated to us that the same is true of animals" (1).

Let us compare with this Schwann's very similar but vastly more celebrated statement written 15 years later:

"When organic nature (animals and plants) is regarded as a whole in contradistinction to the inorganic kingdom, we do not find that all organisms and all their separate organs are compact masses, but that they are composed of innumerable small particles of a definite sort. These elementary particles, however, are subject to the most extraordinary diversity of figure, especially in animals; in plants they are for the most part or exclusively, cells. This variety in the elementary parts seems to hold some relation to their more diversified physiological function in animals, so that it might be established as a principle that every diversity in the physiological significance of an organ requires a difference in its elementary particles; and, on the contrary, the similarity of two elementary particles seems to justify the conclusion that they are physiologically similar" (4).

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later. In regard to Dutrochet's statement that the 'corpuscles' were in the walls of cells, it may be noted that Schwann emphasized repeatedly that the nucleus is closely attached to the cell wall. Thus when describing the young cells of the chorda dorsalis, he writes: "I have taken great pains to discover a nucleus *in their walls*, but without success. . . . . It must remain a question whether the nucleus is really wanting, or whether it is only not visible in consequence of its translucency" (4). Schleiden also believed the nucleus "to be enclosed in the cell wall, in such a manner that the wall of the cell splits into two laminae, one of which passes exterior and the other interior to the nucleus" (18). On the other hand, the "minute corpuscles" seen by Dutrochet may have been cell granules, appearing through a poor microscope as though at the surface of the cell. Schwann also speaks of "the granulous nature of the cell membrane," and Valentin, as late as 1835, believed pigment granules to be situated on the surface of the pigment cell.

Schwann's knowledge of the finer structure of cells and of the tissues which he studied was undoubtedly much more extensive than was Dutrochet's. While Schwann's descriptions of tissues approach the realm of real histology, Dutrochet admits that he was scarcely able to distinguish microscopically between the different organs; but he did see clearly that all living animal tissues, like those of plants, are composed of myriads of small cells "sometimes arranged in longitudinal and linear rows, sometimes grouped in a confused manner." Although we are not concerned here with the question of the origin of descriptive histology, it must be pointed out that, while Schwann far surpassed Dutrochet in that science, he was by no means the first to describe the details of the cellular structure of individual animal tissues. Müller, Henle, Arnold, Purkinje, Valentin, Turpin, Dumortier and others[8] had ably preceded him in that field at the beginning of the period of widespread interest in the microscope which began about ten years after the publication of Dutrochet's work. Indeed, Schwann was not even the first to discover the cellular nature of most of the tissues discussed in his own celebrated book; Müller had previously described cells in the chorda dorsalis; Purkinje, Deutsch, Gurlt and Meckauer in cartilage; Henle in surface and intestinal epithelium; Hooke and Dutrochet in feathers; Werneck in the crystalline lens; Gurlt, Raspail and others in adipose tissue. Even the familiar "sheath of Schwann" had been seen by the Viennese physiologist Prochaska years before Schwann redescribed it. It must be clear, therefore, that if Schwann's monograph is more detailed from an histological standpoint than is Dutrochet's, Schwann had the advantage of being able to incorporate into it the many studies in animal histology which had accumulated during the fifteen years following the publication of Dutrochet's work, including the very important discovery of the nucleus of fixed-tissue cells. Furthermore, during those fifteen years great strides had been made in the

[8] Although Raspail is traditionally mentioned in this connection, it is probable that most of those who have, themselves, turned the leaves of his "Nouveau Système de Chimie Organique,"—that curious encyclopedic work, sallying into a dozen different fields, and coloured with bitterness, gossip and invective,—have been tempted to concur with Schleiden's opinion that "to enter into a discussion of the work of Raspail would be incompatible with the dignity of science" (11).

improvement of the microscope. It would have been hardly possible for Dutrochet to have seen the details of tissue structure appreciated by Schwann who, even with his much better microscope, placed "the minuteness of the cells" first in his list of difficulties encountered in the attempt to prove the cellular nature of animal tissues. Dutrochet's writings contain remarks which leave no doubt about the inperfections of his microscope. He refused, for example, to believe his eyes when he re-discovered through a microscopic observation, the principle of osmosis, because of the "many well-known optical illusions of which the microscope is the source." In another place he relates that several years after the publication of his cell theory, Amici brought to France for the first time his improved type of microscope. "All those who were interested in the progress of natural science hastened to go to see and to admire this new instrument which was sure to extend and to render more certain our knowledge of the microscopic world." With the better instrument of Amici, a controversy between Dutrochet and Mirbel regarding the existence of pores in the tracheal tubes of plants was easily settled in favor of Dutrochet. I shall enter no further into the discussion of the relative histological knowledge of Dutrochet and Schwann, for it is not the accurate description of the arrangement of the cells in different tissues which constitutes the cell theory, but only the principle that the cell is the anatomical and physiological unit of all living tissues. The above excerpts from Dutrochet's monograph leave no doubt that he was completely aware of the *anatomical* fact of this generalization. The next point to consider is whether or not he appreciated the importance of the cell as the living, *physiological* unit of the tissues. His statements are crystal clear on this score as well:

> "It is within the cell that the secretion of the fluid peculiar to each organ is effected. These fluids are probably transmitted by transudation into the excretory canals. . . . . Thus the cell is the secreting organ *par excellence*. It secretes, inside itself, substances which are, in some cases, destined to be transported to the outside of the body by way of the excretory ducts, and, in other cases, destined to remain within the cell which has produced them, thus playing specific rôles in the vital economy" (1).

Then follows a highly interesting foreshadowing of the idea of internal secretion:

"One can scarcely doubt that parenchymatous organs (such as the spleen) which have no excretory duct must, also, manufacture in their cells substances which are destined either to remain within those cells, or to pass into the blood vessels by transudation."

"In each organ," he continues, "the cells must have different characteristics, since such different substances are secreted within them. In this connection, one cannot help admiring the prodigious diversity of the products of living beings—a diversity which is even greater in the plant kingdom than in the animal kingdom. What a variety in the physical and chemical qualities of the substances secreted by the cells which make up the parenchyma of fruits, stems, roots, leaves and flowers in all the plants which cover the surface of the globe! One can scarcely conceive that such an amazing diversity of products results from the activity of a single organ—the cell. When one compares the extreme simplicity of this organ with the extraordinary diversity of its internal powers, it becomes evident that the cell is truly the *pièce fondamentale* of the living organism" (1).

What clearer general statement of the physiological significance of the cell could be desired? And yet in the most important modern treatises on the cell we find only such statements as: "Schwann first gave clear expression to the fundamental conception that, beneath the unending diversity of form and function, all cells conform to a common morphological and physiological type" (13).

Not only did Dutrochet appreciate the cellular nature of living animal tissues; he also made the penetrating discovery that inert solid parts of the body may be divided into two general types: (1) those representing the remains of dead cells, and (2)those which are merely deposits of material outside of cells. In a masterful study "On the Structure and Regeneration of Feathers, with General Considerations on the Composition of the Skin of Vertebrates," published first in 1819, and republished with revisions in his "Mémoires" in 1837, he writes:

"Not all of the solid products of the living body are *organic solids*. Thus, for example, the membrane and the shell of the bird's egg are not formed by a real growth as true organic solids are; they are formed rather by the coagulation or hardening of certain secreted fluids. Microscopic examination reveals no *organic texture* in such solids formed by the hardening of secreted fluids. On the other hand, whenever one finds an *organic texture* in a part of the body, one can without hesitation affirm that that part was once alive, and that it has consequently been

formed by a true growth. Now an *organic texture* can be clearly recognized in all parts of feathers. The spongy substance is made up of a mass of globular utricles. It is a true cellular or utricular tissue resembling the cellular tissue which is seen in certain parts of plants; it is, in a way, an *animal cork*. . . . . In its origin, therefore, the feather is a part of the living organism of the bird. It is then very soft, and it remains alive as long as it preserves its softness. It loses its life when it becomes dry and hard. Thus the well developed feather represents an originally living structure which has suffered death by desiccation."

"Life exists, at least with any degree of activity, only when the elementary substances contained (in the cells) are in fluid form."

It may be remarked that in the foremost modern medical histories, as well as in numerous other books, it is *Schwann* who is named as the discoverer of the feather-cell![9]

Dutrochet, further, recognized clearly that important fact, the re-enunciation of which brought great glory to Schleiden years later—namely, that growth consists only in the increase in the number and the size of cells.

"Growth results both from the increase in the volume of the cells, and from the addition of new little cells," he writes. And, again, after citing numerous observations in support of this idea: "It is evident, therefore, that (during growth) new, rudimentary cells are formed, which, by increasing in size, finally become cells such as those which have preceded them in order of appearance and development."

It is a matter of particular interest that Dutrochet, during his cellular studies, discovered the phenomenon of the migration of the leucocytes and was the first to apply to them the term "wandering cells." He describes this observation as follows:

"I have several times seen blood cells which had escaped from the circulatory stream stop and remain stationary in the tissues. I have witnessed this phenomenon, which I was previously far from suspecting even, while observing the movement of the blood with the microscope in the transparent tails of tadpoles of the obstetrical toad. . . . . Between the loops of the blood

[9] Strictly speaking, not even Dutrochet can claim that distinction, for Robert Hooke, himself, after describing the cellular structure of the pith of feathers, wrote in 1667: "I guess this pith which fills the Feather . . . . to be a kind of solid or hardened froth, or a *congeries* of very small bubbles consolidated, in that form, into a pretty stiff, as well as tough concrete, and that each Cavern, Bubble, or Cell is distinctly separate from any of the rest" (6).

vessels there is a very transparent tissue in which one sees many granular bodies about the size of blood cells. Now, while watching the motion of the blood, I have several times seen a single blood cell escape from the side of the blood vessel and move off into the transparent tissue with a slowness which contrasted strongly with the rapidity of the circulatory stream from which the cell had escaped. Soon after, the cell stopped moving and remained fixed in the transparent tissue. . . . . In what way do these cells get out of the blood stream? That is not easy to determine. Perhaps the vessels have openings in their walls through which blood elements can escape into the tissues; perhaps the movement of the cells was first slowed and finally stopped completely because they became caught within blood vessels relatively too small for them. One may explain it as one will, but the fact will remain forever proven. I have observed it too many times to believe that it was only an accidental phenomenon. This phenomenon is undoubtedly one in the order of living nature." After suggesting that fixed-tissue cells may be derived in this manner from blood cells, and that the escape of the leucocytes into the tissues may be associated with a nutritive function, he describes the blood cells as "wandering cells (*cellules vagabondes*) which end by joining themselves to the tissues of organs" (1).

This constitutes the first observation of the motility and the migration of the leucocyte. Nearly half a century elapsed before Cohnheim rediscovered the phenomenon and recognized its importance in inflammation.

When we approach the subject of Dutrochet's attempt to understand the *mechanism* of cellular metabolism we come at once upon one of his most important contributions to physiology—the application of the physical principle of osmosis to living processes. In 1748, the Abbé Nollet, during the course of his experiments on the cause of ebullition, filled a flask with alcohol, covered the mouth with a piece of bladder, and immersed it in a vessel of water. Several hours later, he noticed that the membrane was bulging outward very distinctly. He reversed the experiment, filling the flask this time with water and immersing it in alcohol; the surface of the membranous covering now became concave, as though driven inward. Nollet suggested that these effects might be the result of a greater permeability of the membrane for water than for alcohol, and thought no more of the matter. About fifty years later, Porret divided a vessel into two compartments with a piece of bladder. He filled one of the compartments with water and put only a very little into the other. After a lapse of several hours no change had occurred in the

level of the fluid in either compartment. He next placed the negative pole of a battery in the full compartment, and the positive pole in the other, and saw that the water then passed rather rapidly through the membrane from the former into the latter. He was quite at a loss to understand this phenomenon, and merely recorded it. About 1812, Soemmering discovered that when a mixture of water and alcohol was placed in a vessel made of a distended bladder, the alcohol became concentrated because of the evaporation of water from the external surface of the bladder. He reasoned from this that water passes through such a membrane more easily than alcohol, but his conception of the importance of the observation seems to have centered in the fact that, thenceforth, the small householder, equipped only with a pig's bladder, could transform cheap, diluted liquors into elixirs of desirable proof. None of these investigators regarded what they observed as anything more than a peculiar trick of nature, and the fact of the existence of such a force as osmosis lay as dead and unnoticed as though it had never been discovered. In 1826, Dutrochet rediscovered the phenomenon under conditions which suggested to his alert and prepared mind the significance of it in organic nature. The part played by osmosis in physiological processes is one of such fundamental importance that I do not hesitate to reproduce here the original description of the curious and penetrating observation which, exactly one hundred years ago, led Dutrochet to the recognition of the activity of this force in the operation of vital processes:

"In a bowl of water I had a little fish, the tail of which I had cut off. On the surface of the wound there developed a sort of aquatic mould with rather long filaments, at the end of each of which there was a bulbous swelling easily visible with the naked eye. I was stirred with curiosity to observe with the microscope this plant which was growing upon a living animal. The filaments of the mould were transparent, but the terminal swellings, which were pointed at the end and resembled the capsules of plants, were completely opaque. I cut off a few of these filaments and placed them in a watch-glass containing water in order to study them under the microscope. I saw that soon a multitude of little globules were expelled from an opening at the tip of each of the opaque capsules. As these globules were expelled, the lower part of the capsule (that part opposite the tip from which the globules were discharged) became empty. The globules remaining in the upper part of the capsular cavity seemed compressed together and forcibly driven upward by an accumulation of water in the lower part of the capsule. The fact that

this empty part of the capsule had not decreased in size made it clear to me that the expulsion of the globules was not due to a contraction of the capsule. The water, which had entered the lower part of the capsule, seemed to have acted like the piston of a syringe in driving upward and forcing out from the tip some of the globules with which the capsule was originally completely filled. After a few seconds all of the globules were driven out of the capsules, which were then filled only with water, having lost none of their original size. . . . . Whence came this water? What was the force which made it enter the capsules? . . . . It was necessary for me to place this phenomenon in the category of those of which the cause is entirely unknown. Since the observation was made with the microscope, its accuracy could be questioned by those who are familiar with the many optical illusions of which that instrument is the source. I contented myself, therefore, with making a note of it; and I thought no more about it until a similar observation, this time not requiring the use of the microscope, presented itself. It was, in this instance, the animal kingdom which furnished the material" (3).

The second observation consisted in noting that the sperm sacs of snails, when placed in water, explode and expel their contained spermatozoa as a result of the imbibition of water, in a manner quite comparable to the expulsion of the spores from the capsules of the little aquatic plant.

"These were the two observations which led me to establish the existence of a new physico-organic force. . . . . I shall designate this force . . . . by the term 'endosmosis,' a word derived from ἔνδου meaning 'within' and ωσμος, meaning 'impulsion.'"

Immediately after the second of these observations, Dutrochet began his long series of ingenious experiments on osmosis. He filled with milk a sac made of a loop of the intestine of a chicken, immersed it in water, and found that it gained weight by the imbibition of water. In order to determine whether such membranes allow the passage of water in only one direction, he used other sacs made of inverted intestines. Under similar conditions they, too, imbibed water and gained weight. It occurred to him then that the difference in the densities of the solutions on either side of the membrane might be a factor in determining the passage of fluid through it. He therefore filled his intestinal sacs with water, immersed them in milk, and rejoiced to find that they then *lost* weight because of the passage of water to the outside medium. He varied these experiments, using

different forms of membranes, acids and alkalis, and solutions of many different salts. Sometimes he colored his solutions in the effort to trace the direction of the fluid current more easily. The results led undeviatingly to the formulation of the principle that when an organic membrane is placed between solutions of unequal density, there will occur a passage of fluid through the membrane, and that the direction of this fluid current will always be toward the denser of the two solutions. He was not aware of the existence of semipermeable membranes, the properties of which were not investigated by Pfeffer until fifty years later. He observed, however, that the denser solutions also diffuse through membranes toward the less dense, but with much less rapidity. He termed this phenomenon "exosmosis," and considered it as a force similar to but much less powerful than "endosmosis." He made an effort to discover some connection between electrical activity and osmosis, and always believed osmosis to be, at bottom, the result of electrical forces. He invented an "osmometer" for the purpose of measuring the osmotic force of different solutions and the rapidity of their diffusion; but his greatest contribution in connection with osmosis was his recognition of its importance in physiological processes.

For a mind occupied with cellular problems, and which had had no difficulty in jumping from the filament of a mould to a sac made of a chicken's intestine, the recognition of the analogy between the intestinal sac and the individual sac-like tissue cells was a matter of course. Dutrochet became so deeply impressed with the power and possibilities of this new force that, as it commonly enough happens, his first enthusiasm caused him to stress its importance excessively. He described it in the title of his report as "L'Agent immédiat du mouvement vital." He, himself, however, with his customary self-honesty, wrote some years later: "I know that at first I went too far in considering endosmosis as the fundamental phenomenon of life—as its active principle"(2).

Dutrochet's concept of metabolism can be gathered from the following quotations which, aside from containing the first application of the principle of osmosis to the explanation of physiological processes, are very interesting from a more general standpoint. It will be remembered that Bichat, faced with the problem of explaining

the nutrition of tissues and the discharge of waste from them, had assumed the existence of innumerable minute, vascular terminations of two different types (*absorbant* and *exhalant*), all arising from capillaries and ending in open communication with the tissues (14). Dutrochet's microscopic studies of the circulation in living animals several years before, had made him thoroughly familiar with the appearance of the capillary circulation, and he refused to accept Bichat's theoretical explanation. He now realized that his newly-found phenomenon would enable physiologists to dispense forever with that convenient, but purely fantastic, assumption:

"In animals with a circulatory system, the blood vessels ramify among the cells which make up the various tissues. The cells lie along the walls of the blood vessels, but it is certain that the interior of the cell is not in direct communication with the lumen of the blood vessels, for they each contain different fluids. This fact is very easy to verify by examining microscopically the tissue of a secretory organ of a gasteropod mollusc, that of the liver, for example. One sees that the cells of this organ are filled with bile which can be recognized by its color, while the blood vessels which border these cells are transparent because of the colorless blood which they contain. Thus the blood vessels serve only as a means of irrigation for the elementary cells, and it is only by filtration that the plasma can penetrate into them. The blood system, considered in its entirety, forms a closed cavity into which nothing can enter and out of which nothing can escape except by filtration. The so-called 'arterial tips' and 'venous rootlets' are physiological fables. The absolute continuity of arteries and veins is plainly visible with the microscope in very young salamanders. . . . . These are the vascular ramifications which effect the irrigation of the organs, carrying to their elementary cells new organic materials which are transmitted to the cells by filtration, and that in virtue of endosmosis as we shall show.

"The soft tissues are aggregates of cells, filled ordinarily with a pasty substance which is more dense than the blood plasma which bathes their walls, or is separated from them only by the extremely thin walls of the capillaries. As a result of this arrangement the blood plasma must tend continually to enter the cells, which become then the seats of two electric currents, one, the stronger, producing endosmosis, and another, the weaker, producing exosmosis. Through the effect of endosmosis the substances in the blood are forced into the cells; exosmosis brings it about that the cells return to the blood-stream a part of the solution which they contain. The effect of exosmosis is favored and strengthened by the pressure which results from the forced entry of external fluids into the already full cells. Thus an equilibrium must be established between the introduction and the expulsion of fluids, in spite of the difference which exists between the energy of the two electric currents to which endosmosis and exosmosis are due" (3).

In regard to the internal activities of the cells he writes:

"The separation of the chyle from the fecal matter with which it is mixed in the intestines is a true *chemical filtration*. The intestinal mucous membrane, a true chemical filter in this respect, permits the passage of only those substances possessing particular qualities. This activity may be considered as a sort of *secretion*, but in this case the secretory activity consists only in the separation of mixed substances. From this point of view it is analogous to the secretion of urea by the kidneys, for it is known from the experiments of Prévost and Dumas that urea exists ready formed in the blood. All secretions are not simple separations of mixed substances however; most of them are the results of a separation followed by a new association of the elements contained in the nutritive plasma. . . . . The substances thus secreted are finally discharged from the cells, partly through the effect of exosmosis, and partly because of the continual entry of fluids due to endosmosis. This discharge occurs normally in the direction of the excretory ducts, but if these ducts are accidently obstructed, the secretion is discharged into the blood vessels, leading in most cases to various morbid conditions" (3).

Thus was fulfilled, in an unexpected manner, the prophesy of Robert Hooke who, a century and a half before, wrote after unsuccessful attempts to find holes in the cell walls through which the nutritive fluids could pass: "Methinks it seems very probable that Nature has in these passages, as well as in those of animal bodies, very many appropriated Instruments and Contrivances whereby to bring her designs and end to pass, which, 'tis not improbable, but that some diligent Observer, if helped with better *Microscopes*, may in time detect" (6).

While Schwann hardly touched the question of the manner in which substances enter, are changed by, and leave the cell during metabolism, he devoted a very large part of his book to his erroneous theory of the manner of origin of new cells. Dutrochet, on the other hand, having observed nothing which gave him a clue as to the way in which new cells are formed, contented himself with stating that he was unable to determine whether they arose within pre-existing cells, or by the "development and extension" of pre-existing cells, or by a new formation out of the intercellular substance. He did, however, make an important general discovery on the relation of the blood vessels to the growth of cells, which is erroneously attributed to Henle, who reached the same conclusion in his work on epithelium in 1837. This was the observation that blood vessels are not directly

necessary for the growth of animal cells. For years it had been stated and believed that a fundamental difference between animals and plants lay in the fact that in the animal body, as contrasted with the bodies of plants, the immediate presence of blood vessels was absolutely necessary for the growth of any tissue. In his studies upon the regeneration of feathers Dutrochet wrote:

"The fact that, in the feather, nutrition and growth proceed in spite of the absence of blood vessels in its organic tissue, proves that the blood vessels are not necessary for the phenomenon of nutrition. They act only as a means of irrigation for the tissues of organs. They furnish by filtration the nutritive fluid which the tissues make use of in their nutrition and growth. . . . . The nutritive fluid is in the same way poured out into the organic interstices and it is from these that the living parts with which it is in contact take it up to use it in their growth" (2).

Although Schwann was a clear-headed scientist, he was also devoutly religious—indeed, to the extent of refusing to print his book containing the cell theory until he had first submitted it to the church authorities for examination and approval. However, the brave stand which he made for science, in the face of the tenets of his church, at the time when he became involved, in an unfortunate manner, in the celebrated case of the stigmatized Louise Lateau, allows one to suspect that the disapproval of the church would hardly have been sufficient to have prevented him from printing the book. In a lengthy philosophical discussion at the end of it, he succeeded, apparently to his satisfaction from both a religious and a scientific standpoint, in working out a concept of the universe in which the Deity was excluded from any interference in the operations of Nature. He then felt free to speculate about life in as mechanistic a fashion as he chose, and he indulged this freedom to such an extent that he has often been referred to as the father of the modern mechanistic doctrine.

"To Schwann belongs the honor," writes Frédéricq, "of having been the first among the pupils of Johannes Müller to have formulated the principles of the mechanistic theory of life, and to have developed the consequences systematically" (15).

Schwann's frequently quoted summary of his mechanistic concept is as follows:

"We set out, therefore, with the supposition that an organized body is not produced by a fundamental power guided in its operation by a definite idea, but

is developed, according to blind laws of necessity, by powers which, like those of inorganic nature, are established by the very existence of matter. Since the elementary materials of organic nature are not different from those of the inorganic kingdom, the source of the organic phenomena can reside only in a different combination of those materials" (4).

Strangely enough, even in this last field, that of mechanistic philosophical speculation, the forgotten Dutrochet preceded and surpassed the celebrated Schwann. The mechanistic concept of life was second nature to him. His writings on this subject, full of prophetic insight, have, after the lapse of a hundred years, a thoroughly modern ring:

"The generally accepted opinion that life is due to some agent entirely foreign to inorganic nature has always appeared to me to be unworthy of the philosophy of science."

"The discovery of osmosis links physics to physiology for all time. By means of it I have been able to explain the mechanism of most of the movements which occur in certain parts of plants." Then, citing his experiments on the rôle of oxygen in living animals, he continues: "In all these different circumstances I have seen the laws of general physics preside over the activity of different physiological phenomena. These first attempts in the application of physical phenomena to the explanation of physiological phenomena tend to dissipate the *mysteries* which the vitalistic physiologists have introduced into physiology. The time is not far distant, I hope, when we shall see the occult and mystical forces, which are now used to explain vital phenomena, replaced by the exposition of the physical laws to which those phenomena are really due. One will no longer say that the organs *call* fluids to them, and *choose* from them the particular substances which they *desire* for their nutrition or absorption. All these *psychomorphisms* will disappear in the face of facts which will bring together, under the empire of physical laws, the physiological phenomena which men have tried to separate from that empire."

"If we are unable at present to explain all of the phenomena of life on the basis of physical laws it is merely because the laws of physics are not all known. Living processes fall, for the most part, into the category of molecular movements, and these generally escape measurement, and, consequently, calculation, our surest means of arriving at certainty. Thus the fundamental laws which govern molecular movements remain necessarily unknown to us. But if we must, for the present, renounce knowing the fundamental laws which govern living processes, it is however permitted to us to recognize the chain which binds those processes as *effects* to various known physical *causes*. I do not doubt that the progress which is being made at present in the application of the knowledge of electricity to problems dealing with the molecular movements of bodies or with chemical affinities,

will eventually throw great light upon the many phenomena of vital chemistry which occur in the living body. Physiology will thus find itself united both to physics and to chemistry. Already I have tried, and, I dare to believe, with some measure of success, to link physiology and physics by applying the physical phenomenon of endosmosis to the explanation of certain physiological phenomena, especially in plants."

"The physiological connections which I have established between plants and animals make it clear that there is but a single physiology, a general science dealing with the functions of living beings,—functions which vary in their modes of execution but which are fundamentally identical in all organized beings. I hope that some day, out of these first attempts, there will be born a new science—*general physiology*" (2).

As far as I am able to determine, this is the first use and definition of that term so familiar today on the covers of reference books and research journals in all countries—"General Physiology."

V

In all branches of human thought, it is a familiar fact that important new concepts which the age is not advanced enough to understand, may either be scorned and rejected, or else left unnoticed and ignored for years, until they are restated by a second writer at a more favorable time, immediately thereafter to become appreciated and lauded. Such instances are by no means unknown in the domain of medical science; but it is popularly believed that, in cases of this nature, the original discoverer must have published his work in an obscure place; or that he perhaps did not appreciate the significance or application of it himself, and consequently failed to emphasize its importance; or that he probably described his observations vaguely and unimpressively; or that his proofs may have been insufficient, requiring amplification by the later investigator. As a matter of fact, cases of delayed appreciation occur in which none of those explanations are applicable. That this is true is illustrated in a most striking way by the fate of three of Schwann's works, namely, the formulation of the cell doctrine, the discovery of the organic nature of the agent of alcoholic fermentation, and his beautiful experiments directed against the theory of spontaneous generation. All three of these works were published within a period of three years; all were written in the same clear, forceful style; and all were printed in outstanding journals. From the standpoint of sufficiency of proof con-

tained in them, the paper on the cell theory is, without question, more unsatisfactory than either of the other two; for, aside from the deluge of errors which it contained, this paper announcing the cellular composition of *all* tissues, does not mention a microscopical observation on a single parenchymatous organ save the kidney. On the other hand, Schwann established, in the clearest manner, by ingenious chemical and morphological observations, the fact that the cause of alcoholic fermentation is a living organism. He even watched it grow by multiplication under the microscope. Yet it is common to read today that "in 1857 *Pasteur* decisively proved that fermentation was a physiological process, for he showed that the yeast which produced fermentation was no dead mass, as assumed by Liebig, but consisted of living organisms capable of growth and multiplication" (16). As for his work on spontaneous generation, it is always something of a shock to those of the present age who happen upon Schwann's extraordinary but forgotten paper, published in 1837, to discover in it an account of the most beautifully controlled and conclusive experiments of the very nature of those for which the genius of Pasteur has for so long been admired. Thus, in Schwann, we have a rather remarkable example of the fact that it is not *who* announces a truth, nor *how*, nor *where;* but rather *when* it is announced, which may be the deciding factor in the spread of that truth. For in the single person of Schwann we see an investigator who became immortal by uttering an unoriginal statement at the proper time and, on the other hand, remains almost forgotten in relation to his own most brilliant discoveries. It is significant that, in explanation of the general lack of appreciation of Schwann's fundamental work on fermentation and spontaneous generation, one of his most celebrated contemporaries wrote merely the expressive phrase "die Ungunst der Zeiten" (17).

In science, as in politics and other fields of human endeavor, the mere forceful declaration of a great generalization may be powerless to shape, instantly, the thought of the time. It has often been remarked that the time must already hold the idea in a state of supersaturation before the concrete expression of it can produce its immediate and widespread crystallization. When such a state of "supersaturation" exists, in which many minds are interested in

various aspects of a particular idea, and vaguely suspect its true outlines, a definite enunciation or restatement of it is often all that is required to make a hero of any accidental person.

Now Dutrochet and Schwann both communicated their researches to the Paris Academy of Sciences; both assembled their observations in monographs, even the titles of which were very similar. As evidences of Dutrochet's clarity and forcefulness of expression, his thoroughness of treatment and emphasis of the fact and significance of the cellular composition of tissues, the above quotations from his works will serve. But in 1824, when Dutrochet published his observations, practically no one was interested in the minute study of animal tissues. Few, indeed, of his contemporaries had ever looked through the microscope at any part of the animal body. On the other hand (as has been pointed out above) in the early thirties, before the appearance of Schwann's monograph, great improvements were made in the construction of the microscope. There promptly arose in Germany, largely through the influence of Johannes Müller, a widespread interest in the microscopical study of animal tissues, and much unrelated information regarding their cellular structure was rapidly accumulated. "Those were the fortunate days," wrote Henle in 1882, "which the present generation may well envy us . . . . for it was then still possible to make a fundamental discovery by merely scraping an animal tissue with the blade of a knife, or with the finger nail" (17). The nucleus of plant cells, which had previously been regarded as an accidental curiosity, was recognized to be a normal part of the cell by the eminent botanist, R. Brown, in 1832, and was soon thereafter described by numerous observers in animal tissue cells as well. This little morphological hall-mark went far toward paving the way for the acceptance of the idea that plant cells and animal cells are fundamentally alike.

In 1838, Schleiden, a botanist trained in law and medicine, who later renounced science for philosophy, and to whom is commonly, but erroneously, ascribed the discovery of the general principle of the cellular composition of plant tissues, published his brief "Contributions to Phytogenesis," a paper which is, in many places, almost unintelligible today because of the profusion of errors of observation

and deduction which it contains.[10] The purpose of that paper was to demonstrate that the growth of plants consists in the formation of new cells, especially within pre-existing ones, by a sort of crystallization of nuclei out of the cytoplasm of the original cell, and the subsequent formation of fresh cytoplasm about each new nucleus. Undeserved emphasis is frequently laid upon Schleiden's supposed penetration of the fact that all new cells arise from pre-existing ones. His observations on that subject are almost completely erroneous; and, furthermore, although it is never mentioned, he did not hesitate to describe in the same paper another totally different and even more imaginative method of formation of new cells: "Beneath the outermost layer of cells which are comprised in the term bark, an organizable fluid is poured out, as it were, into a single, large intercellular space, which fluid, it seems, consolidates quite suddenly throughout its entire extent into a new, altogether peculiarly-formed tissue of cells, which are deposited one upon another, the so-called prosenchyma. Here, moreover, there is decidedly no formation of vascular bundles from cells of lower dignity, for all of them originate simultaneously and of their full size" (11). Yet this is the paper which is universally regarded as one of the two great foundation stones of the cell doctrine, and because of which the names of Schleiden and Schwann will continue to alliterate, inseparably, down the centuries.

Schwann was at this time only 27 years old, but he had already to his credit a series of five fundamental discoveries, any one of which could have insured his immortality. Müller had just suggested that he study the cellular nature of the chorda dorsalis, and, being a close friend of Schleiden, and thoroughly familiar with the latter's views on the origin of plant cells, he decided to see whether he could establish a similar method of origin for animal cells. "The whole of the foregoing investigation," he wrote in the concluding chapter of his celebrated monograph, "has been conducted with the object of ex-

[10] If this judgment of Schleiden's work appears heretical, I can only urge the reader to examine for himself not the traditional reviews of it, but the original paper itself. Virchow, commenting upon the remarkable fact that it was possible for the foundations of scientific progress to be built upon works so full of errors as those of Schleiden and Schwann, made a similar plea as long ago as 1882. He lamented even then that "Man erzählt eben nach, was man hört, aber man hält sich nicht mehr für verpflichtet, die Quellen zu durchforschen" (5).

hibiting, from observation alone, the mode in which the elementary parts of organized bodies are formed." This, not primarily the demonstration of the cellular nature of animal tissues (with which fact he freely admitted many of his contemporaries were familiar[11]) was his chief purpose, and his supposed accomplishment of it his chief pride. "The principal result of this investigation." he wrote, "is that one common principle of development forms the basis of all organized bodies" (4). He went even further astray on the subject, however, than his predecessor Schleiden, for he believed that he saw a crystallization of new nuclei not only within pre-existing cells, but also outside of cells in the intercellular fluids. Neither Schleiden nor Schwann had the remotest idea of the vital necessity of the nucleus. "As a general rule," wrote Schleiden, "it is rarely that the nucleus accompanies the cell which it formed through its entire vital process." Schwann's observations led him to concur with Schleiden's opinion that the nucleus is eventually absorbed and disappears. Schleiden and Schwann were thus both concerned primarily with the problem of cellular origin, but their contemporaries, ready and waiting rather for the formal declaration of the principle that *all living tissues are composed of cells*, ignored their most serious efforts and immortalized them because their writings contained statements about the cellular nature of tissues, which, however unoriginal, were, nevertheless, required at that moment to effect the crystallization of the cell doctrine. If we sought to extract the most worthwhile statement contained in each of these papers, we would find simply this: Schleiden stated that all plant growth consists in the formation and expansion of new cells; and Schwann, that the cell is the anatomical and functional unit of all living tissues, whether of animals or of plants. Dutrochet had previously announced both of these facts. It is true that Schleiden and Schwann observed the presence of cells in the young embryos of plants and animals, respectively; but it must be pointed out that Schleiden's belief that cells can arise *en masse* by a sudden wide-spread crystallization, and Schwann's belief in the crystallization of cells from the intercellular substance, rob their observations

[11] Indeed, a number of Schwann's contemporaries (among them Purkinje and Valentin) did not hesitate to point out that, in their written works, they had preceded Schwann in directing attention to the cellular nature of animal tissues, and in comparing the microscopic appearance of animal cells with those of plants.

on the embryo of any claim to having established the important fact that all of the tissues are composed of cells derived from the original fertilized egg-cell. As for the manner of origin of cells, it required the work of nearly two more decades before the descriptions of cell division, especially by Remak, Kölliker, and Virchow, established the familiar aphorism—*omnis cellula e cellula;* and it was not until 1873 that the process of mitosis was unravelled by Schneider.

There is one last question to consider: Was Schwann acquainted with Dutrochet's monographs? In his meagre historical sketch of the "state of the matter when I commenced my researches," he quotes no work prior to 1835, and not once in his entire monograph does he mention the name of Dutrochet. Nevertheless, there are three things which are at least suggestive of the possibility that he had read Dutrochet's work. The first of these is the fact that he, as well as Dutrochet, reported his investigations to the Paris Academy of Sciences; it is therefore probable that he was acquainted with the more important publications of that body. In the second place, the words "endosmosis" and "exosmosis," newly created by Dutrochet, are to be found in Schwann's monograph. Finally, there are several instances, such as the following, in which Schwann uses similes so identical with those used by Dutrochet in the same connections, that it is at least a very interesting phenomenon if the minds of these two men really functioned independently in the same manner in such a wide variety of circumstances:

Dutrochet	*Schwann*
"The spongy substance (of feathers) is made up of a mass of globular utricles. It is a true cellular or utricular tissue resembling the cellular tissue which is seen in certain parts of plants; *it is, so to speak, an animal cork.*"	"The pith of feathers is seen to be composed of beautiful polyhedral cells, which perfectly resemble the parenchymatous tissue of plants—*as, for example, the substance of cork.*"

Again, in a discussion of the filter action of the cell membrane:

Dutrochet	*Schwann*
" . . . . in this case the secretory activity consists only in the separation of mixed substances. From this point of view *it is analogous to the secretion of urea by the kidneys,* for it is known . . . . that urea exists ready formed in the blood."	"The secretion of substances already present in the blood, *as, for instance, of urea, by the cells which line the urinary tubules,* cannot be explained without such a faculty of the cells."

I can find no evidence that, during his life, Dutrochet ever sought to shift the glory of having first proclaimed the cell theory from Schwann to himself by directing attention to his own earlier work; and I have no illusions as to the possibility (even if the accomplishment of it were desirable) of overturning a popular idol by merely pointing out that the particular revelation for which he is most worshipped is, after all, not an original one. My purpose is rather to recall the name and the achievements of Dutrochet on this, the one hundred and fiftieth anniversary of his birth; and, having brushed the accumulated dust from his several books, forgotten on the shelves of medical libraries, to allow their pages to be illuminated for a brief moment by the light of an age capable of appreciating them.

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BOOK REVIEWS

Review of the Diagnosis, Treatment and End Results of Tuberculous Disease of the Hip Joint. By GEORGE PERKINS, 118 pp. $1.75. (*Oxford Medical Publications, Humphrey Milford, London, 1926.*)

This monograph on tuberculosis of the hip has been excellently worked up and is well worth reading. It is most worthy of the award of the Robert Jones Prize. It is a thorough inquiry into the treatment and end results of 50 cases. No attempt has been made to cover the subject from every aspect.

Emphasis is laid on the early diagnosis of the condition. There are very clear radiographic pictures of the different types of disease, such as that involving the acetabulum, the head and the neck of the femur, which deserve especial attention and study. The head was affected in 80 per cent of the cases studied. Emphasis is laid on the non-operative treatment (recumbency, traction and fixation), and the general treatment (open air, hygiene and heliotherapy). The only operative treatment recommended is an arthrodesis of the joint in selected cases. In the final results studied all of the patients have been under the care of the surgeon for years. Stress is laid on the fact that once a doctor has undertaken to treat a case of tuberculosis of the hip, the patient should be followed for a lifetime.

A detailed description of the Pyrford Frame used in the treatment of this disease is given. This is a combination of the Bradford Spinal Frame and the Jones Abduction Hip Splint. A special carriage for the transportation of the patient to the outside is shown, called the Carshalton Carriage. Mention is made of Diaplyte—the Dreyer Vaccine for tuberculosis, but it is thought to be of no value in treating tuberculosis of the joints.

A. R. S., JR.

Modern Methods of Feeding in Infancy and Childhood. By DONALD PATERSON and J. FOREST SMITH. 106 pp. $3.00. (*Paul B. Hoeber, New York, 1926.*)

The importance of breast feeding is rightly emphasized and the use of many proprietary foods for infant feeding is explained. The tables of analyses of various types of milk and patent foods and the descriptions of their composition will be helpful to those who prescribe these diets.

A. E. F.

Methods in Surgery. By GLOVER H. COPHER, M.D. 232 pp. $3.00. (*The C. V. Mosby Company, St. Louis, 1925.*)

This book which covers the various routine and special procedures employed on the Surgical Service at the Barnes and the St. Louis Children's Hospital will

be of value to those especially interested in hospital methods. Locally it should serve a very useful purpose, but it is of little general interest.

W. A. N.

The Crippled Hand and Arm. By CARL BECK. 243 pp. $7.00. (*J. B. Lippincott Co., Philadelphia, 1925.*)

The scope and object of the book is to study the various conditions which interfere permanently with the physiologic activity of the hand and arm.

The author first discusses the congenital deformities of the hand and fingers and reviews the classical operations for their correction. Injuries to the hand caused by infection are discussed and wide opening of infected areas alongside the anatomical channels advocated. By numerous illustrations and citations of individual cases the author demonstrates what can be done by the conservative treatment of mutilating injuries of the fingers. These data should be especially interesting to those engaged in industrial surgery.

In the second part of the book are enumerated and discussed the various bone, joint, nerve, and tendon injuries that cause "the crippled hand." Illustrated cases of tendon and nerve injuries with detailed steps in the operative procedure for their correction are given.

The last chapter in the book is devoted to the technique of skin-grafting. The photographs and drawings are good.

B. M. B.

Diseases of the New-born. By DR. JOHN A. FOOTE. 231 pp. $5.00 (*J. B. Lippincott Co., Philadelphia, 1926.*)

Dr. Foote and his associates have written an admirable summary of the problems confronting the practitioner in dealing with the newly-born infant. They have discussed, in no exhaustive fashion, to be sure, the accidents that may happen to the infant during delivery, the care of the normal infant, the commoner diseases occurring in neo-natal life, their diagnosis and treatment. Of particular value at this time is his chapter devoted to a detailed description of the technical procedures with which one must be familiar in handling infants. To the pediatrist the volume will seem incomplete and in places, because of its brevity, dogmatic; to the general practitioner and the obstetrician who by circumstance may be forced to care for his newly-born infants it will prove of invaluable aid.

A. J. S.

Epilepsy. A Functional Mental Illness. By R. G. ROWS and W. E. BOND. Pp. 136. $3.00. (*Paul B. Hoeber, New York, 1926.*)

The authors briefly review the various theories which have been proposed for epilepsy and decide, with good reason, to reject them all as unsatisfactory. The gross anatomical changes which have been described are inconstant and the microscopic lesions are probably secondary. Therefore, they approach the problem from a new angle. Their conclusions in brief are that the one element

which is common to all epileptic seizures is a disturbance of consciousness with which is associated an emotional state. The clonic movements of the convulsion are merely an expression of the emotion. Different emotions are expressed in different types of fits. The cause of the seizure is the revival of a memory which had some emotional value. Vasomotor changes also occur in emotional states and, the authors fancy, vasomotor reactions must also occur in the brain. As they put it, "The equivalent of a blush may occur within the skull." The repetition of these physiological vasomotor reactions, if too intense or if repeated too often, gives rise to sclerosis and other morbid changes in the brain. The processes of inhibition and facilitation are evoked to account for the repetition of the attacks which soon become conditioned reflexes. The authors' material was apparently largely composed of ex-service men some of whom had suffered head injuries. The evidences upon which they base their conclusions are the results obtained by analysis of the patient's mental content before and after the seizures. If his last thoughts were of some apparently neutral topic, it was always easy to develop an association with some thing more important from the analytic point of view. In many cases the authors were able to uncover memories of war experiences, usually of a terrifying nature. In their opinion, all types of epileptic phenomena are equivalent. Therapy, they believe, must consist of explanation, exploration, reëducation. They state vaguely that "the fits disappeared on treatment by psychic exploration and explanation," and "the fits ceased after working out the mental cause," but do not say how many patients were cured and how long the "cures" lasted.

To the reviewer the book seems wrong from cover to cover. In the first place, the statement that disturbance of consciousness is the characteristic feature of epileptic phenomena is open to doubt, since every neurologist is familiar with focal attacks during which consciousness is not altered. It is hard for anyone who has observed the so-called "drop" seizures, which occur without an instant's warning, to be convinced that any definite emotional state precedes their onset, and equally hard to conceive of the clonic convulsion as the expression of various emotional states. It does not astonish us to hear that association tests performed on disabled soldiers soon after the war should reveal unpleasant memories of the war, but it is astonishing to find that their convulsions are attributed to these memories. It does not seem probable, to say the least, that infantile epilepsy can be explained by a similar mechanism. The statements that vasomotor nerves supply the cerebral vessels and that vasomotor reactions occur in the brain during emotions are unsupported by any known facts. The claim that such physiological reactions result in organic lesions in the brain is not only entirely hypothetical but inherently improbable. It is obvious that experimental work with bacterial toxins is inapplicable to this problem. The close connection between convulsions and brain lesions, such as the infantile hemiplegias in which epilepsy follows in 50 per cent of all cases, cannot be ignored. No one with medical experience is ignorant of the connection between chemical changes in the blood in tetany, uremia, puerperal

eclampsia, and convulsions. In brief, the authors' hypotheses are unsupported by any evidence and are at variance with what little is known of epilepsy.

F. R. F.

The International Clinics. Vol. II. 36th Series. Edited by Henry W. Cattell, A.M., M.D. 314 pp. $3.00. (*J. B. Lippincott Co., Philadelphia, 1926.*)

The International Clinics—Vol. II—June 1926, has arrived with its usual assortment of instructive topics appealing to a wide interest.

Dr. Feiling of London presents the changes in the fundus oculi found in the examination of "one-hundred unselected and consecutive cases of hyperpiesia, arteriosclerosis and chronic renal disease," in which defective vision was the chief, if not the only, complaint of the patient. The predominant changes found include:—retinitis, 22 cases; thrombosis of the retinal veins, 18 cases; macular disease (degenerative and exudative), 11 cases; papilloedema, 7 cases; and retinal arteriosclerosis, 8 cases.

Dr. Fremont-Smith in a clinic on "Cord Tumor" adds this condition to a formidable list of extra-abdominal causes of abdominal pain. The sharp localization of the pain, its exacerbation on coughing and sneezing, together with tenderness over neighboring vertebral spinous processes are mentioned as important diagnostic features.

Dr. Moses presents interesting and exceptional blood chemistry findings in a number of cases of nephritis—particularly some rather low blood creatinin figures. Fuller autopsy reports would add much to the value of the data presented. On page 188 it is stated, "The following history demonstrates that all patients in coma from the kidneys do not show high retention of urea." There is nothing included in the subsequently added data to this case which would prove beyond peradventure that the patient in question really died of "coma from the kidneys."

The book has many other worthy features not the least of which is a charming account of "The Conquest of Yellow Fever" by Colonel F. A. Winter.

E. H. H.

The Surgery of Gastro-Duodenal Ulceration. By CHAS. A. PANNETT, B.S.C., M.D. (Lond.), F.R.C.S. (Eng.). 154 pp. $3.25. (*Oxford Medical Publications, Humphrey Milford, London, 1926.*)

This little monograph covers a very interesting field of surgery which has been and is still a great source of active controversy. The author discusses all phases of his subject in a very clear, conservative and rational manner, using excellent illustrations and skiograms liberally. The book should be a useful asset to any surgeon's library.

W. D. N.

Laboratory Outlines in Bacteriology and Immunology. By J. F. NORTON and I. S. FALK. 114 pp. $2.00. (*The University of Chicago Press, Chicago, Ill., 1926.*)

The "Laboratory Outlines in Bacteriology and Immunology" is to be a guide for the instructor in the arrangement of courses and at the same time a help for the student in taking up the course. The book represents briefly a clear and comprehensive schedule of the important and recent tests in Bacteriology and Immunology. The technic of the proposed tests is precisely given and well defined. The results and their interpretation are left to the instructor, but frequent explanatory notes concerning the various problems are given. The first part of the book is an introduction to Bacteriology from a broad general standpoint and the second part deals skilfully with serological problems. The choice of the experiments is excellent.

I. D.